Menopause and the Brain: Maximizing Cognitive and Psychological Well-being at Midlife

Pre-Meeting Symposium
Wednesday, October 5, 2016
7:30 AM - 1:00 PM
Marriott Gaylord Palms Hotel
Orlando, Florida

Held in advance of the 2016 Annual Meeting of The North American Menopause Society
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<td>8:00 AM – 8:10 AM</td>
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<td><strong>Pauline M Maki, PhD</strong></td>
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<td>8:10 AM – 9:45 AM</td>
<td><strong>Part 1 — Mood</strong></td>
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<tr>
<td>8:10 AM – 8:35 AM</td>
<td>Natural History of Mood Changes Across the Menopause Transition</td>
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<td><strong>Joyce T Bromberger, PhD</strong></td>
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<td>8:35 AM – 9:00 AM</td>
<td>Neurobiology of Mood Changes During the Menopause Transition</td>
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<td><strong>Claudio N Soares, MD, PhD, FRCPC, MBA</strong></td>
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<td>9:00 AM – 9:25 AM</td>
<td>Assessment and Treatment of Depression in Menopause</td>
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<td><strong>Susan G Kornstein, MD</strong></td>
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<td>9:25 AM – 9:45 AM</td>
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<td><strong>Part 2 — Cognition</strong></td>
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<td><strong>C Neill Epperson, MD</strong></td>
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<td>11:00 AM – 11:25 AM</td>
<td>Screening and Treatment of Cognitive Complaints in Midlife</td>
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<td><strong>Victor W Henderson, MD, MS, NCMP</strong></td>
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<td>11:25 AM – 11:45 AM</td>
<td>Interactive Panel Discussion With Q&amp;A</td>
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<td>11:45 AM – 12:00 PM</td>
<td>Break and Box Lunch Distribution</td>
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<td>12:00 PM – 12:25 PM</td>
<td><strong>Part 3 — Sleep</strong></td>
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<td>12:00 PM – 12:25 PM</td>
<td>Sleep in the Menopause Transition</td>
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<td><strong>Hadine Joffe, MD, MSc</strong></td>
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<td>12:25 PM – 1:00 PM</td>
<td>**Part 4 — Case Presentations With Interactive Panel Discussion and Q&amp;A</td>
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The North American Menopause Society (NAMS) 2016 Pre-Meeting Symposium has been planned and implemented in accordance with the Accreditation Council for Continuing Medical Education’s (ACCME) Essential Areas and Elements, as well as its Standards for Commercial Support.

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Intended Audience

This activity is intended for physicians, nurses, nurse practitioners, physician assistants, pharmacists, and other members of healthcare teams that treat or counsel women at midlife and beyond.

Overall Educational Objectives

At the conclusion of this activity, participants should be able to

- Assess cognitive and mood changes in menopausal women
- Treat depression, anxiety, and cognitive complaints in menopausal women or refer appropriately

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Other healthcare professionals who participate in this activity will receive a certificate of participation. NAMS has determined that this activity includes a maximum of 2.0 hours of pharmacotherapeutics education.

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- **Planners and reviewers**: Recused from planning or reviewing an activity if they cannot contribute to an unbiased, evidence-based view of the clinical options to be presented in the material. If there is a relevant financial interest, NAMS ensures that planners and reviewers without a relevant financial interest will also participate in reviewing or planning the activity.

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Joyce T Bromberger, PhD
Professor of Epidemiology and Psychiatry
University of Pittsburgh, Graduate School of Public Health
Pittsburgh, Pennsylvania

Natural History of Mood Changes Across the Menopause Transition

It is well known that depression is a significant problem for women. Two broad domains of risk factors have been the focus of efforts to understand women’s vulnerability to depression: reproductive hormone activity and psychosocial characteristics. Research suggests that women’s risk for depression is greater during periods of alterations in patterns of ovarian hormone production. However, whether the risk for depression is elevated during the menopause transition (MT), a time of dynamic and changing reproductive hormone activity, has been uncertain. At the same time, psychological, social, and environmental factors, some specific to or more prevalent in midlife and the MT, are known to contribute to the development of depression in women.

The Study of Women’s Health Across the Nation (SWAN) evaluated longitudinally the natural history of mood changes during the MT. SWAN found that depression symptoms and disorder are more likely to occur during the MT than during premenopause. Despite the increased depression risk, only a subset of women are susceptible to mood alterations during the MT. It has been hypothesized that some women are particularly sensitive to CNS exposure to female reproductive hormone fluctuations. To what extent women’s reproductive physiology and neurobiology explain the risk remains unclear. Additional risk factors include stress, limited social support, sedentary behavior, limitations in health and functioning, early life adversity, and history of depression. Each of these contributes independently to depression. We need to learn more about the specific effects of risk factors during a period of biological vulnerability to increase our ability to identify women susceptible to MT mood changes.

ACKNOWLEDGMENTS

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Neurobiology of Mood Changes During the Menopause Transition

It is undeniable that depression can be a complex, multifaceted phenomenon, particularly during midlife years. It is most likely affected by age, comorbid conditions, cardiovascular and metabolic issues, vasomotor and sleep changes, ethnicity, lifestyle behaviors (eg, physical activity, smoking), and stressful life events.

Clinicians and researchers have long debated the existence of reproductive-related windows of vulnerability for depression across a woman’s life cycle. Essentially, some (but not all) women would be particularly sensitive to develop mood changes while facing disruptions in their hormonal milieu. The controversy surrounding the existence of a menopause-related depression exposes some misinformation and confusion on this topic; heterogeneous or even inaccurate criteria have been used to define menopause staging or characterize psychological stress, mood symptoms, or depression. Moreover, anxiety and sleep problems—commonly cited as contributing factors to depression—are rarely included as key outcome measures in well-designed, properly powered treatment studies.

Estrogen has been suggested by some as beneficial to mood because of its overall effects on synthesis, metabolism, and receptor density/activity of neurotransmitters such as serotonin and norepinephrine. Estrogen therapies have shown antidepressant effects of similar magnitude to that observed with classic antidepressants but mainly among perimenopausal women—suggesting a window of opportunity for the effective use of estrogen-based strategies for depression.

New studies and techniques will shed some light onto the neurobiology of depression in midlife years, including functional imaging tasks combined with estrogen-based antidepressant interventions and assessment of peripheral markers (inflammatory, oxidative) in perimenopause before and after development of depressive symptoms.
Assessment and Treatment of Depression in Menopause

A National Network of Depression Centers task force has been formed to develop guidelines for the assessment and management of depression in the menopause transition. This talk will discuss the recommendations of the task force regarding diagnostic assessment and differential diagnosis as well as treatment considerations.

Depression during the menopause transition presents with classic depressive symptoms, usually in association with menopause-specific symptoms and psychosocial stressors. Depression and somatic symptoms characteristic of the menopause transition may overlap and compound each other. Psychosocial challenges of midlife may include children leaving home, aging and loss of parents, and illness in oneself and one’s spouse. The differential diagnosis of the mood disturbance includes adjustment disorder, major depressive disorder, psychological distress, subsyndromal depression, bereavement, and bipolar depression.

Treatment approaches for depression during the menopause transition include antidepressants, estrogen therapy, psychotherapy, and other modalities. Antidepressants are the first-line treatment choice and may also be beneficial for vasomotor symptoms. Differences in antidepressant efficacy by menopause status have been reported for some medications. Estrogen therapy has been shown to be efficacious for perimenopausal (but not postmenopausal) depression, although the data are limited. Nevertheless, for a patient presenting with significant and bothersome vasomotor symptoms and depression, an initial brief trial with estrogen therapy (transdermal estradiol) could be considered in order to determine its benefits and tolerability for the treatment of both mood and menopause symptoms. If depressive symptoms remain, then antidepressant treatment is recommended.
Pauline M Maki, PhD
Chair, 2016 Scientific Program Committee
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, Illinois

Natural History of Cognitive Changes Across the Menopause Transition

Memory complaints are among the top three most frequently acknowledged symptoms on menopause-symptom questionnaires. Prospective cohort studies demonstrate that memory performance declines as women transition through the menopause, even after controlling for advancing age. Initial findings suggest that memory performance rebounds during the postmenopause stage.

What role might menopause symptoms play in cognitive symptoms during menopause? Although mood also worsens during the menopause transition and is generally associated with worse cognitive performance, mood symptoms do not account for declines in memory during the transition. Similarly, although memory complaints are associated with vasomotor symptoms (VMS), numerous studies indicate that VMS are unrelated to performance on objective tests of memory.

In contrast, an association between VMS and memory performance is observed when VMS are measured with ambulatory skin conductance monitors rather than by self-report. Physiologic VMS, but not reported VMS, are also associated with alterations in brain structure and function.

Neuroimaging studies provide insights into the brain changes that accompany the menopause transition. These studies show that the function and structure of the prefrontal cortex and hippocampus vary with menopause stage. Estradiol plays a central role in cognitive and brain changes during the transition; memory declines after oophorectomy and pharmacologic suppression of ovarian steroid hormones but rebounds with estrogen therapy. Recent clinical trials show that hormone therapy is not effective maintaining cognitive function in naturally menopausal women treated early in the postmenopause period, but trials have not targeted perimenopausal women or women with moderate to severe VMS.
Reproductive hormones exert a profound effect on neurochemistry, neuronal and glial structure, and brain function. Central nervous system structures critical to cognition, such as the prefrontal cortex and hippocampus, are targets for ovarian and adrenal steroids. Additionally, ovarian hormones such as estradiol are known to modify the effects of stress on these brain structures. Finally, women’s genetic profiles with respect to various neurotransmitter synthesis and metabolizing enzymes may contribute to their susceptibility to cognitive changes during the menopause transition.

The prevalence of significant cognitive changes and whether these are solely subjective and not objectively discernible is still an area of ongoing debate. However, it is clear that early and abrupt loss of ovarian hormones contributes to increased risk. New evidence suggests that executive function complaints, specifically, are amenable to treatment with stimulant medications, such as those approved for attention-deficit hyperactivity disorder. Brain imaging studies also suggest that stimulant-induced changes in brain chemistry and neural activity may be key to their capacity to improve subjective outcomes. Given that women are living at least a third of their lives postmenopause, it is important for clinicians to have a working understanding of how the brain is altered during the natural, surgical, or medically induced transition to menopause in order to address their patients’ concerns regarding their long-term cognitive health.
Screening and Treatment of Cognitive Complaints in Midlife

Cognitive abilities change over a lifetime. For some domains, the magnitude of decline can be substantial. This is particularly so for tasks that assess episodic memory and executive functions. Because cognitive complaints are common in midlife, the clinician’s challenge is to distinguish age-related changes without important functional or clinical significance from changes that suggest underlying neurological, medical, or psychiatric disorders and those that reflect unhealthy lifestyle practices.

The general approach is to identify specific contributors to cognitive symptoms, to ameliorate those that can be improved, and to promote healthy brain aging (Maki P, et al. Menopause 2016;23:803-805).

For the midlife patient with cognitive symptoms, the clinician must first decide whether there is objective decline beyond that associated with normal aging. Contributory neurological and medical disorders should be screened for and excluded, but these will be uncommon. Depression, anxiety, vasomotor symptoms, sleep disorders, midlife stressors, and effects of medications or alcohol are more common and are amenable to treatment.

Brain health is enhanced above all by factors that sustain vascular health. These include smoking cessation and prevention or treatment of hyperlipidemia, hypertension, and diabetes. Regular aerobic activity, mental activity, and social engagement may benefit cognitive aging. The Department of Health and Human Services offers useful guidelines on physical activity (www.health.gov/paguidelines).

Hormonal changes associated with the menopause transition and postmenopause are relevant but not necessarily paramount. There are small changes in cognitive performance across the menopause transition not fully accounted for by age. However, large clinical trials in early postmenopausal women suggest no important cognitive effect of estrogen-containing hormone therapy, with the caveat that comparable trial data are unavailable for women still in the menopause transition. Further, it is not known whether midlife hormone therapy influences the risk of late-life Alzheimer disease. Observational studies imply a protective association, but the interpretation is controversial, and hormone therapy initiated later in life increased dementia risk of Women’s Health Initiative participants randomized to receive conjugated estrogens plus medroxyprogesterone acetate.
Sleep disturbance is a core symptom of the menopause transition. Women are more likely to experience problems sleeping, in general, and specific sleep disorders in particular during perimenopause and postmenopause than during their reproductive years. Common causes of sleep disturbance linked with the menopause transition include hot flashes, sleep apnea, insomnia, depression, and restless legs/periodic limb movement disorder. Other factors include age-related sleep changes and medical conditions. These conditions can co-occur and may be difficult to untangle. Evaluation of sleep disturbance in midlife women involves ascertaining the nature of the sleep complaint and obtaining an overnight sleep study where indicated. Studies of menopause-related sleep problems have advanced our understanding of the causes and optimal treatments for this common condition. Treatment considerations vary with the type of the sleep disturbance and include therapies targeting nighttime hot flashes, sleep hygiene, cognitive behavioral therapy for insomnia, hypnotic agents, and treatments for primary sleep disorders of sleep apnea. Data bearing on the leading causes of sleep disturbance during the menopause transition and treatment options for these conditions will be reviewed.
Faculty

Joyce T Bromberger, PhD
Professor of Epidemiology and Psychiatry
University of Pittsburgh, Graduate School of Public Health
Pittsburgh, Pennsylvania

C Neill Epperson, MD
Director, Penn Center for Women’s Behavioral Wellness
Professor, Department of Psychiatry and Obstetrics and Gynecology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Victor W Henderson, MD, MS, NCMP
Professor, Departments of Health Research and Policy and Neurology and Neurological Sciences
Stanford School of Medicine
Stanford, California

Hadine Joffe, MD, MSc
Associate Professor, Harvard Medical School
Associate Professor, Brigham and Women’s Hospital
Director, Women’s Hormone and Aging Research Program
Director of Research Development, Department of Psychiatry
Director, Division of Women’s Mental Health
Brigham and Women’s Hospital
Director, Psycho-Oncology Research
Department of Psychosocial Oncology and Palliative Care
Dana Farber Cancer Institute
Boston, Massachusetts

Susan G Kornstein, MD
Professor, Psychiatry and Obstetrics and Gynecology
Executive Director, Institute for Women’s Health
Virginia Commonwealth University
Richmond, Virginia

Pauline M Maki, PhD
Chair, 2016 Scientific Program Committee
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, Illinois

Claudio N Soares, MD, PhD, FRCPC, MBA
Professor of Psychiatry
Queen’s University School of Medicine
Kingston, Ontario, Canada
Executive Lead, Canadian Biomarker Integration Network for Depression (CAN-BIND)
St. Michael’s Hospital, University of Toronto
Toronto, Ontario, Canada