Jointly provided by University of Louisville Continuing Medical Education & Professional Development and Global Academy for Medical Education

www.globalacademycme.com

CLICK FOR CREDIT®

Stay up to date on important developments in research and practice recommendations and earn CE/CME credit by reading the articles that follow. All posttests must be completed and submitted online.

Original Release & Termination Dates
Medium or combination of media used: Written and online enduring material activity.
Method of Physician Participation: Written and online articles.
Estimated time to complete the educational activity: 15 minutes per article.
Course Originally Released On: 1/1/2016
Course Termination Date: Individual articles are valid for one year from date of publication.

Hardware & Software Requirements for Online Participation: High speed Internet connection; Adobe Acrobat 7.0 or higher; course content compatible with Mac OS.

Click For Credit® Program Overview: Provision of the highest quality medical care requires that clinicians remain up-to-date on important developments in research and practice recommendations. Click For Credit is part of a multi-year initiative to stimulate continuous learning of new developments in the clinical practice of medicine. Articles selected for the Click For Credit educational activity provide a convenient avenue for accessing current information and incorporating relevant concepts into patient care.

Claim CME/CE Credit
1. Review the program information, including the disclosure statements
2. Read the entire article
3. Access the article on www.globalacademycme.com site by using the URL provided at the end of the article
4. Correctly answer the post-test questions
5. Complete the evaluation form
6. Follow the instructions for printing or e-mailing your CME/CE credit certificate. Transcript summaries of your activities or additional copies of certificates are available by clicking the Your CME/CE Activity Transcript button.

Peer Reviewer: Lisa Joan Pfitzer, MD
Assistant Professor, University of Louisville School of Medicine; Chair, University of Louisville Continuing Medical Education & Professional Development Advisory Board

Dr Pfitzer has no relevant financial relationships with any commercial interests.

Joint Provider Statement

University of Louisville Continuing Medical Education & Professional Development

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Louisville and Global Academy for Medical Education, LLC. The University of Louisville is accredited by the ACCME to provide continuing education for physicians.

Designation Statement
Physicians: The University of Louisville Office of Continuing Medical Education & Professional Development designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AMA PRA accreditation begins January 2015. Term of approval is for 1 year from this date. Credit may be claimed for one year.
[Physician assistants may claim AMA PRA credit.]

Nurses: This program has been approved by the Kentucky Board of Nursing for 0.3 continuing education credits through University of Louisville Hospital, provider number 4-0068-7-16-811. The Kentucky Board of Nursing approval of an individual nursing education provider does not constitute endorsement of program content.
[Nurse practitioners may claim these credits.]

Target Audience
This enduring activity is intended for family medicine physicians, internal medicine specialists, related specialists, residents, nurses, and other healthcare professionals who are most likely to be consulted for treatment of various diseases and disorders that comprise healthcare in primary care medicine.

Learning Objectives: On completing this educational activity, participants should be able to:
- Discuss the results of the study or educational presentation addressed in these articles which focus on topics of high clinical interest for physicians, physician assistants, nurses, nurse practitioners who are in clinical practice.
- Review the clinical relevance and practice implications of the information presented.

Commercial Support: No commercial support was used or received to fund this enduring material.

Disclosures: The staff members of Global Academy for Medical Education report that they have no financial disclosures to report. Disclosures relevant to each article are included in or with the individual Click For Credit articles.

There is no fee to participate in this activity. Costs associated with this activity are borne by Global Academy for Medical Education as a service to physicians and the healthcare community at large.

Course Director Joseph F. Fowler, Jr., MD has no relevant financial relationships to disclose.

Coordinator Sylvia H. Reitman, MBA, DipEd has no relevant financial relationships to disclose.
Planning Committee Members: W. Daniel Cogan, EdD, Sylvia H. Reitman, MBA, DipEd, and Jenny Campano have no relevant financial relationships to disclose.

Faculty
Disclosures relevant to each article are included in or with the individual Click For Credit articles.

University of Louisville Continuing Medical Education and Professional Development Staff and Advisory Board
The CME & PD staff and Advisory Board have nothing to disclose with the exception of Dr Douglas Coldwell: Sirtex, Inc. (Speaker) and DFine, Inc. (Consultant).

Special Services: If you need an alternative form of course materials due to a disability, please contact s.reitman@globalacademycme.com. Continuing Medical Education & Professional Development fully complies with the legal requirements of the ADA and the rules and regulations thereof.

Provider Contact Information: If you need technical support or have questions about the course, please e-mail us at cmepd@louisville.edu

Privacy Policy: The University of Louisville's Continuing Medical Education and Professional Development office respects your privacy. Personal information collected from participants of our medical educational activities will not, unless required by law, be shared with any third party. The primary reason we collect your personal information is for accountability and documentation of your continuing education activities in compliance with Accreditation Council for Continuing Medical Education (ACCME) regulations. We do not distribute unsolicited e-mails, nor, unless required by law, do we share the names of our subscribers with any third party.

Click For Credit articles are originally published by Frontline Medical Communications family of publications (www.frontlinemedcom.com).

turn page to get started >>

Later Menopause Lowers Risk for Later Depression

Michele G. Sullivan

The longer a woman's reproductive years last, the less she may be prone to postmenopausal depression, a large meta-analysis has determined.

The risk for depression declined by 2% for every two premenopausal years after age 40. Women who entered menopause after age 40 experienced a 50% decrease in the risk for depression, compared with women who experienced premature menopause, Dr. Marios K. Georgakis and colleagues reported in *JAMA Psychiatry* (2016. doi:10.1001/jamapsychiatry.2015.2653).

The findings suggest that longer exposure to endogenous estrogens mediates the pathophysiology of late-life depression, wrote Dr. Georgakis, of the National and Kapodistrian University of Athens, and coauthors.

"If confirmed in prospective and culturally diverse studies ... these findings could have a significant clinical effect by allowing for the identification of a group of women at higher risk for depression who may benefit from psychiatric monitoring or estrogen-based therapies."

The meta-analysis comprised 14 studies that included 67,714 women. They controlled for numerous factors, including age, BMI, obesity, smoking status, and hormone therapy use. However, only two controlled for past depression—one of the biggest risk factors for recurring depression.

In addition to the 2% decline per two premenopausal years after 40, a subanalysis of three studies examining severe depression found a 5% decreased

VIEW ON THE NEWS

Observations, but not proven links

The study is a commendable effort to examine the role of reproductive hormones in postmenopausal depression, but several important caveats should temper enthusiasm for its conclusions, Dr. Hadine Joffe and Joyce T. Bromberger, PhD, wrote in an accompanying editorial. In most of the studies, women were ages 55 to 60—considerably beyond the average menopausal age of 52. Additionally, most were at least five years past their menopause, reflecting a group that might have passed the period of highest risk for hormone-mediated depression.

This meta-analysis does not address depression associated with the gonadal steroid fluctuations of perimenopause or recent estradiol withdrawal of immediate postmenopause, the colleagues wrote. Rather, the analysis applies to depression in older women whose brains have not recently been exposed to estradiol or other reproductive hormones and for whom hormonal risk factors have previously been considered less relevant.

The study is one of the few to investigate the psychotropic effects of estrogen on aging women, however. In contrast to the acute effects of reproductive hormones on mood in cycling women, the article highlights a potential neuroprotective effect of gonadal steroids on mood that is delayed and extends into the stable hypoestrogenic and hypoprogestinemic environment of postmenopause. Its conclusions are strengthened by studies of nonpsychiatric diseases associated with earlier menopause, including cardiovascular disease, cognitive decline, and dementia.

Nevertheless, it's too early to recommend prophylactic hormone therapy, the authors concluded. Given the small effect size and limitations of the studies used in this analysis, more direct evidence supporting a sustained and delayed neuroprotective effect of extended exposure to estradiol, cyclic progestins, and their neurosteroid derivatives is required to support use of hormonal therapy as a therapeutic approach to protecting against postmenopausal depression.

Dr. Joffe is Director of the Women's Hormone and Aging Research Program at Brigham and Women's Hospital, Boston. **Dr. Bromberger** is a Professor of Epidemiology and Psychiatry at the University of Pittsburgh.

risk for the same time measure. Another analysis of women with premature menopause found a doubling in the risk for depression for those who experienced menopause before age 40.

Estrogen is known to have neuroprotective and antidepressive properties, and the brain is richly endowed with estrogen receptors, the authors said. The exact pathway of protection against depression, however, remains unknown. Potentiation of neurotransmitters and moderation of atherosclerosis might play protective roles.

"Given the results of our study, it remains to be investigated whether women with menopause at younger ages could benefit by preventive use of hormone therapy against late-life depression, provided that adverse effects associated with long-term use are considered," the authors said. "In this context, the development of estrogen receptor subtype–specific ligands could decrease the proportion of estrogen therapy adverse effects."

Disclosures: *Neither Dr. Georgakis nor any of the coauthors declared any financial conflicts.*

To take the posttest, go to **http://bit.ly/1U7I7f3** and click Click for Credit® *Expires January 6, 2017*

Preschool ASD Prevalence Estimates Lower Than Grade School Estimates

Tara Haelle

Estimated prevalence of autism spectrum disorder (ASD) among 4-year-olds falls short of the estimated prevalence among 8-year-olds in a recent study comparing nationally representative age cohorts.

"Because previous reports indicate that many children with ASD are not evaluated until after age 4, ASD prevalence in this 4-year-old age cohort will likely rise when measured at a later age," Deborah L. Christensen, PhD, of the CDC, and her associates reported. "Lowering the age at first evaluation may be more relevant than lowering the age at diagnosis, given the challenges of diagnosing young children with ASD," they wrote (*J Dev Behav Pediatr.* 2016;37[1]:1-8).

The investigators screened health and education records for all 4-year-old and 8-year-old children participating in five of the 11 sites involved in the 2010 Autism and Developmental Disabilities Monitoring Network, an active surveillance system for identifying 4-year-olds with ASD. The authors looked for an ICD billing code and/or special education data that included an ASD diagnosis or a description of "behavior consistent with ASD."

They then compared autism prevalence, cognitive test scores, demographics, and ages of evaluation and ASD diagnosis among the 58,467 4-year-olds and 56,727 8-year-olds assessed, each cohort representing approximately 1.4% of those age-groups in the 2010 US population.

Prevalence of ASD among 4-year-olds was 13/1,000 children overall, approximately 30% lower than prevalence estimates for 8-year-olds and ranging from a low of 9/1,000 in Missouri to a high of 20/1,000 in New Jersey. Other states involved in the analysis included Arizona, Utah, and Wisconsin. Prevalence was significantly higher in states with both education and health records available than in those states with only health records available.

At all five sites, boys significantly proportionally outnumbered girls in ASD diagnosis. Overall, three

boys had ASD for every one girl with ASD, but the ratio varied from 2.6 in Arizona, Missouri, and Wisconsin to 4.4 in New Jersey. Despite no overall difference in ASD prevalence by race/ethnicity among 4-year-olds, white 8-year-olds had 1.4 times greater prevalence than that among black children and 1.2 times greater prevalence than that among Hispanic children the same age.

Among the 70% of children in Arizona, New Jersey, and Utah who had data on cognitive assessments, 46% of 4-year-olds and 28% of 8-year-olds had cognitive impairment, defined as a score of 70 or lower. Prevalence of both ASD and cognitive impairment among 4-year-olds was 6/1,000 children, compared with 5/1,000 children among 8-year-olds. Prevalence of ASD without cognitive impairment was 7/1,000 among 4-year-olds and 12/1,000 among 8-year-olds.

A history of developmental concerns before age 3 existed for 93% of the 4-year-olds and 87% of the 8-year-olds with ASD. In addition, 71% of the 4-year-olds and 43% of the 8-year-olds had received their first comprehensive evaluation by 36 months.

Disclosures: *The CDC funded the research. Dr. Christensen and her associates reported no disclosures.*

To take the posttest, go to
http://bit.ly/24Mec0X
and click Click for Credit® *Expires January 5, 2017*

VIEW ON THE NEWS

Prevalence disparities by age may increase

In the article by Christensen et al in the *Journal of Developmental and Behavioral Pediatrics,* it is reasonable to hypothesize that the 30% lower rate found for 4-year-old children, compared with 8-year-old children, may be an underestimate of the discrepancy. Recent surveillance reports from the CDC show a marked increase in prevalence, compared with the report from two years earlier. Therefore, by the time the children who were age 4 in 2010 reached age 8, the prevalence difference may be even greater.

When considering differences in prevalence at age 4 and age 8 in the context of record-review surveillance methodology, two distinct questions must be considered: Is all ASD detectable at early ages, meaning are symptoms at clinically significant levels at the time of assessment? Do records adequately capture all cases that have detectable ASD symptoms?

It is evident from the literature that comorbidities, such as intellectual disability (ID), and co-occurring medical and neurologic conditions, such as seizure disorders or genetic syndromes with dysmorphology, are likely to impact the age at which ASD symptoms are evident. It is likely that not all children with ASD demonstrate clear impairment before age 4. Children who do not show ID may be able to compensate for weaknesses in social engagement when the demands are lower but may show increasing difficulties as the social demands increase with age and maturity.

The second question addresses whether available records are adequate for capturing the total number of children affected by ASD. If children have not yet been identified as needing evaluation or intervention services, these records may not exist by age 4. Because evidence indicates that observation by experts is not adequate to detect risk for ASD, these data showing that many children are not captured in record review surveillance at age 4 should compel us to adopt strategies to maximize early detection.

These comments were excerpted from an editorial by **Diana L. Robins, PhD**, of the AJ Drexel Autism Institute at Drexel University in Philadelphia (*J Dev Behav Pediatr*. 2016;37[1]80-82). Dr. Robins reports being co-owner of M-CHAT, which licenses use of M-CHAT for commercial products. She did not receive any royalties connected with this article.

Long-term PPI Use Linked to Increased Risk for Dementia

Heidi Splete

Long-term use of proton pump inhibitors (PPIs) was significantly associated with later diagnoses of dementia in adults ages 75 and older in a prospective cohort study of more than 73,000 individuals. The findings were published online in *JAMA Neurology.*

Overall, the risk for incident dementia was 44% higher among the 2,950 patients who received regu-

lar PPIs, compared with 70,729 who didn't receive PPIs (hazard ratio [HR], 1.44), according to Willy Gomm, PhD, of the German Center for Neurodegenerative Diseases in Bonn, and his colleagues.

To assess the potential link between PPIs and dementia, the researchers reviewed data from a German insurance database during 2004-2011. The study population included 73,679 community-dwelling adults ages 75 and older who were free of dementia at the start of the study (*JAMA Neurol.* 2016 Feb 15. doi: 10.1001/jamaneurol.2015.4791). The patients taking PPIs were slightly but significantly older than those not taking PPIs; there was a higher proportion of women ($P < .001$ for both groups). PPI users were also significantly more likely than nonusers to have a history of depression, stroke, coronary disease, and use of polypharmacy ($P < .001$ for each).

Risk for incident dementia decreased with age, from 69% for patients ages 75 to 79 to 49% among those ages 80 to 84 and 32% among those ages 85 and older.

In addition, the risk for dementia was not significantly different based on specific drugs in a subgroup analysis of the three most often prescribed PPIs: omeprazole, pantoprazole, and esomeprazole. HRs were 1.51, 1.58, and 2.12, respectively.

"If PPIs have adverse effects, it is important to be aware of them," Dr. Daniel E. Freedberg of Columbia University, New York, said in an interview. "When PPIs are indicated, the preponderance of data indicate that their benefits outweigh their potential risks. Clinicians should reassure patients that this was a single study and that previous studies have reached different conclusions. Clinicians should focus on whether or not PPIs are indicated rather than on PPI side effects."

Dr. Freedberg also noted several key limitations of the study: "First, the authors were unable to adjust for crucial variables that might explain a noncausal link between PPIs and dementia. For example, lower socioeconomic status is an established predictor of dementia and may also be associated with PPI use. However, the authors could not capture socioeconomic status.

"Second, patients who use PPIs have more frequent and more intensive health care interactions than patients who do not use PPIs. These patients are thus also more likely to be diagnosed with dementia. This is another source for bias that the authors were not able to capture. Third, clinicians should be aware that this study was designed to compare extremes of PPI use," Dr. Freedberg emphasized.

In addition, "In the primary analysis, patients were classified as exposed to PPIs only if they received at least one PPI prescription every three months for an 18-month period. Patients who used occasional PPIs were excluded from the study," said Dr. Freedberg.

"The present study can only provide a statistical association between PPI use and risk for dementia," the researchers noted. "The possible underlying causal biological mechanism has to be explored in future studies."

Disclosures: *The researchers had no financial conflicts to disclose.*

To take the posttest, go to **http://bit.ly/1nrCdsb** and click **Click for Credit®** *Expires February 24, 2017*

VIEW ON THE NEWS

Challenging research lies ahead

The researchers have provided an important and interesting challenge to evaluate the possible association between use of PPIs and risk for dementia. Further determinants of whether PPIs are causal for dementia require validation in large cohorts and probably in well-designed case-control studies with good measures of long-term PPI use, covariates, and especially methods to measure incidence of dementia.

Dr. Lewis H. Kuller is affiliated with the Department of Epidemiology at the University of Pittsburgh. He made his remarks in an accompanying editorial and had no financial conflicts to disclose.

continued on next page >>

>> continued from previous page

Elevated Cardiovascular Risks Linked to Hidradenitis Suppurativa

Bianca Nogrady

Reprinted with permission from *Cutis* (2015;96[suppl 1]:1-10).

The inflammatory skin disease hidradenitis suppurativa is associated with significantly increased risks for adverse cardiovascular outcomes, such as ischemic stroke, myocardial infarction (MI), and cardiovascular mortality, according to results of a population-based study.

A population-based cohort study of 5,964 patients with hidradenitis suppurativa showed that, after adjusting for confounders such as age, sex, smoking, and other comorbidities, hidradenitis suppurativa was associated with a 57% greater risk for MI, 33% greater risk for ischemic stroke, 53% increase in major adverse cardiovascular events, and 35% increase in all-cause mortality over a mean 7.1 years of follow-up.

The study, published in *JAMA Dermatology,* also showed a significant increase in cardiovascular-associated death, which was the only adverse outcome that remained significantly elevated (incidence rate ratio, 1.58) in patients with hidradenitis suppurativa when compared with a control group of individuals with severe psoriasis (*JAMA Dermatol.* 2016 Feb 17. doi: 10.1001/jamadermatol.2015.6264).

"Studies have suggested that, in hidradenitis suppurativa, atrophy of the sebaceous glands, follicular hyperkeratinization, and subsequent hair follicle destruction are associated with deep-seated inflammation, increased susceptibility to secondary infections, and chronic perpetuation of the inflammatory response," wrote Dr. Alexander Egeberg of the University of Copenhagen and coauthors.

The researchers suggested that there was a "conspicuous absence" of research on the risk for cardiovascular disease in hidradenitis suppurativa, especially in light of accumulating evidence of the association between cardiovascular disease and other chronic inflammatory diseases, such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease.

Disclosures: *No conflicts of interest were declared.*

To take the posttest, go to **http://bit.ly/1nrEFz3** and click **Click for Credit®** *Expires February 17, 2017*