HT & antidepressant response


Summary. There is little doubt that women are at higher lifetime risk than men to develop depression. Overall, the risk for a major depressive disorder is 1.7 times higher among women than men. Because this difference appears to emerge after puberty and declines during the postmenopausal years, it has been postulated that gonadal hormones might play a role in women’s vulnerability to depression and their therapeutic response to antidepressants.

Kornstein et al utilized data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study to examine whether menopausal status and use of hormonal contraceptives or hormone therapy (HT) would have an impact on treatment efficacy among women receiving the selective serotonin reuptake inhibitor (SSRI) citalopram. Premenopausal (N = 896) and postmenopausal (N = 544) women were treated with citalopram for 12 to 14 weeks and had their treatment response and remission assessed with standardized instruments. There were significant differences between these two groups with respect to demographic and clinical characteristics (eg, postmenopausal women were older, more likely to be divorced or widowed, less educated, and less likely to be employed; postmenopausal women also had overall longer duration of illness and greater likelihood of chronicity than premenopausal women). Notwithstanding, no significant differences in treatment efficacy (response, remission rates) were found when menopausal staging and hormone use (either oral contraceptives or HT) were considered.

Comment. Like in other stages of life, depression in midlife women is a complex, multifaceted phenomenon influenced by numerous factors that include comorbid medical and psychiatric conditions, sleep changes, age, ethnicity, body mass index, cigarette smoking, and stressful life events, just to name a few. Kornstein et al were interested in knowing whether treatment outcomes with an SSRI would differ based on menopausal status or the use of hormonal contraceptives or HT. This is a clinically relevant question, particularly in light of previous studies that had indicated a superior response to SSRIs among younger versus older women and among HT users versus nonusers. Moreover, accumulated data suggested the existence of a “window of vulnerability” for the emergence of depression among peri- and early postmenopausal women and indicated a more robust antidepress-
sant response to estrogen-based therapies in perimenopausal versus postmenopausal women. Such observations, along with the current knowledge regarding the effects of estrogen on monoamines that regulate mood and behavior, support the authors’ hypothesis (and the aim of previous investigations) that antidepressant response could in fact differ significantly based on menopausal staging or hormone use.

Ideally, the management of midlife women with depression should require a careful, tailored approach; it should take into consideration the presence and severity of menopause-associated issues (sleep disturbances, vasomotor symptoms, pain) as well as the tolerability and risks of various hormonal and nonhormonal strategies for bone and cardiovascular health, cognition, and mood functioning. This present study serves, however, as a reassurance that even in the absence of such systematic approach, satisfactory results might be obtained with antidepressant agents that are commonly prescribed and generally well-tolerated.

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References:

In analyses adjusted for age, race/ethnicity, diabetes, menopause transition stage, body mass index, smoking, alcohol use, physical activity, medications, prior fracture, and study site, CRP was associated inversely with each composite strength index but not associated with femoral neck or lumbar spine bone mineral density (BMD). A total of 194 women had fractures during the follow-up. Fracture hazard increased linearly with log(CRP) for CRP levels ≥3 mg/L.
in Cox proportional hazards analyses. Addition of any of the composite strength indices did weaken the association and made it statistically nonsignificant. Researchers concluded that, above the threshold of 3 mg/L, fracture risk increases with increasing CRP. Composite strength indices are inversely related to CRP levels, and this partly explains the increased fracture risk with inflammation.

**Comment.** Chronic inflammation is associated with multiple conditions including cardiovascular disease, diabetes, and dementia. Women with osteoporosis are also at risk for cardiovascular disease. It is therefore of interest to study whether fracture risk is associated with inflammation. Elevated levels of an inflammatory marker, CRP, have been associated with increased fracture risk. The mechanism of this association has been unclear because there have been conflicting results on the association of CRP and BMD.

Ishii et al studied 1,872 peri-menopausal community-dwelling women (aged 42-53 y) from the SWAN study with at least one menstrual period in the prior 3 months and tested the hypothesis that the association of CRP with increased fracture risk is mediated by changes in bone strength. Using surrogate markers of femoral neck composite strength derived from bone density studies, they found a modest inverse association (0.035-0.041 SD in bone strength per doubling of CRP). Fracture hazard increased with CRP above a given threshold of 3 mg/L, with no influence of BMD. The authors concluded that composite measures of bone strength are related to CRP and suggested that inflammation plays a role in the risk of fragility fracture.

Why are these findings important? They imply that inflammation plays a role in bone fragility as reflected by composite bone strength indices. The study needs to be replicated in other populations of different ages and using other techniques of measuring bone strength, such as finite element analysis.

Where CRP levels fit in the spectrum of risk factors at this point in time is unclear. Inflammation may be an important part of the risk of secondary osteoporosis in some individuals. The study also points out the differential susceptibility of cortical versus trabecular bone to inflammation, with lumbar spine BMD explaining more of the CRP fracture association than did femoral neck BMD. Lumbar spine, which contains trabecular bone and is highly vascular, may be more susceptible to inflammation-induced bone fragility.

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**Personal histories of atypical femur fractures**


**Summary.** A voluntary, anonymous online survey documented the fracture history of 81 persons nationwide. The mean duration of bisphosphonate treatment in patients was 9.5 years, and prevention was the initial indication in 68% of patients. Ninety-four percent started on alendronate, 77% reported prodromal pain, 16% of these were diagnosed with incident stress fractures, and 39.5% experienced a contralateral atypical femur fracture (AFF). In the 71 patients with AFF, 38% reported delayed healing, 11% had a complete contralateral AFF, and 22% underwent prophylactic rodding for a contralateral stress AFF. In patients with complete AFFs, 44% were continued on a bisphosphonate after the fracture, and 35% underwent a metatarsal fracture. Patients with AFF experienced delayed healing, prodromal pain, and persistent risk of a contralateral and/or other fracture. In patients on long-term bisphosphonates, evaluating femur pain may facilitate early diagnosis of stress AFFs, reducing fracture risk.
Comment. Important clinical lessons can be derived from this review of AFF cases associated with bisphosphonate therapy. Almost all of these cases were seen before the recent FDA guidance regarding the duration of bisphosphonate therapy, as follows:¹

1. The treatment with bisphosphonates should be reserved for patients at high risk of fracture and in whom the benefit-risk ratio is very favorable, in accord with The North American Menopause Society² and National Osteoporosis Foundation guidelines.³ Limit therapy to 3 years (or one dose of zoledronic acid) if used to prevent bone loss in women in early menopause or in those discontinuing estrogen therapy.

2. Review need for continued bisphosphonate therapy after 3 to 5 years. Continue treatment in patients at high risk—those with previous vertebral fracture or those whose bone density is still very low. Discontinue therapy in patients not at high risk.¹,⁴

3. Counsel patients on therapy for more than 3 years to report new thigh pain. If stress fractures or reactions are identified, discontinue bisphosphonates and institute medical and surgical therapy to prevent the occurrence of the complete fracture.

4. If patients on long-term bisphosphonates experience a stress fracture of other bones, perform imaging studies to evaluate the presence of femoral stress reactions.

In the future, we will likely be able to identify by genetic or metabolic testing a subset of patients who are at particular risk for developing atypical femoral fracture while receiving potent antiresorptive drugs. Until then, our improved understanding of the epidemiology and clinical features of these atypical fractures allows us to identify most patients before they experience a complete fracture and, in that manner, limit the risk of long-term bisphosphonate therapy.

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References:

Menopause in BRCA1/2 carriers


Level of evidence: II-3.

Summary. This study examined whether BRCA1/2 mutation carriers have an earlier onset of natural menopause than unaffected women. The subject included 382 white carriers of the BRCA1/2 gene identified within the Breast Cancer Risk Program Registry at the University of California at San Francisco and 765 other white women in northern California. Median age at natural menopause in BRCA1/2 carriers was significantly younger than in the unaffected sample (50 vs 53 y).

The unadjusted hazard ratio for natural menopause was 4.06 (95% CI, 3.03-5.45); after adjusting for smoking, parity, and oral contraceptive use, it was 3.98 (95% CI, 2.87-5.53). For BRCA1/2 carriers who were current heavy smokers (≥20 cigarettes/d), median age at natural menopause was 46 years; for nonsmokers, it was 49 years. BRCA1/2 mutation was associated with a significantly earlier age of natural menopause, and heavy smoking increased the risk, suggesting a risk of earlier infertility in BRCA1/2 carriers.

Comment. The clinical definition of menopause is cessation of cyclic bleeding for 1 year. Al-
though there is marked variability in the onset of menopause, the median age continues to be 51.4 years. Lin et al examine a cellular abnormality that causes the loss of viable follicles by DNA damage in germ cells. Normally, the further action of germ cells may be quiescence, recruitment for development and ovulation, or apoptosis. Without regeneration in the ovary, the follicles are depleted, which leads to a perimenopausal state. This decline may result in infertility and irregularity.

In this carefully documented study, DNA mutations, repair genes, and BRCA1/2 are used as markers. Evidence from many studies indicates DNA repair genes increase the risk of primary ovarian insufficiency. Also, it is assumed that if oocytes are more prone to DNA damage and experience accelerated follicular depletion, this would lead to a higher incidence of infertility and early menopause. The white BRCA1/2 California women had definite spontaneous (natural) menopause onset 3 to 4 years earlier than the other women who were not carriers. Women who smoked had a much earlier onset as well. The authors suggested that the earlier menopause in women with the BRCA1/2 mutation may be because of an even narrower reproductive window, as shown in some statistics for infertility and miscarriage.

Based on these data, healthcare providers consulting these women on fertility may recommend earlier childbearing. The statistics are sound, and the results are documented and explained. Perhaps an important aspect is this study’s design using a marker system to translate the presence of a common problem in women. With increased longevity, the trend for late pregnancies must be questioned in light of these results. Gestation should be reckoned with in any case where early perimenopause is a potential medical hazard.

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New oral medication for vulvar & vaginal atrophy


Summary. The FDA has approved ospemifene (Osphe 60-mg tablets), an oral tissue-selective estrogen agonist/antagonist, for managing dyspareunia caused by vulvar and vaginal atrophy in menopausal women. Ospemifene acts as an estrogen agonist in vaginal tissues. In clinical trials, ospemifene alleviated pain with sexual intercourse and increased vaginal mucosal maturation more than placebo.

Contraindications include estrogen-dependent neoplasia and active or prior venous thromboembolism, stroke, or myocardial infarction. Although ospemifene also acts on the endometrium as an estrogen agonist, no cases of endometrial cancer have been noted in clinical trials. The most commonly reported adverse reactions were hot flashes (8%), vaginal discharge (4%), and muscle spasms (3%). The approval includes a boxed warning about endometrial cancer and cardiovascular disorders.

Comment. Symptomatic vulvar and vaginal atrophy is common but undertreated; thus, new treatment options are welcome. Ospemifene may be particularly appealing to women who prefer not to use vaginal cream, tablets, or the vaginal ring. However, unlike vaginal estrogen therapy, ospemifene is associated with hot flashes and may (like its cousins tamoxifen and raloxifene) raise risk for venous thromboembolism. As with vaginal estrogen, ospemifene’s package labeling does not explicitly recommend concurrent progestin therapy to prevent endometrial neoplasia in women with an intact uterus. However, endometrial monitoring should be considered in long-term users, and any vaginal bleeding should be evaluated. Because ospemifene has not been adequately studied in women with breast cancer, the FDA re-
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Menopause Editor’s picks from March 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.

Coronary heart disease events in the Women’s Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women’s Health Initiative randomized clinical trials.

Robert A. Wild, MD, MPH, PhD; Chunyuan Wu, MS; J. D. Curb, MD, MPH; Lisa W. Martin, MD; Lawrence Phillips, MD; Marcia Stefanick, PhD; Maurizio Trevisan, MD; and JoAnn E. Manson, MD, DrPH.

Hadine Joffe, MD, MSc; Katherine A. Guthrie, PhD; Joseph Larson, MS; Lee S. Cohen, MD; Janet S. Carpenter, PhD, RN, FAAN; Andrea Z. LaCroix, PhD; and Ellen W. Freeman, PhD.

Semara Thomas, MD; Roberta B. Ness, MD, MPH; Rebecca C. Thurston, PhD; Karen Matthews, PhD; Chung-Chou Chang, PhD; and Rachel Hess, MD, MS.

♦ Effects of bazedoxifene alone and with conjugated equine estrogens on coronary and peripheral artery atherosclerosis in postmenopausal monkeys.
Thomas B. Clarkson, DVM; Kelly F. Ethun, DVM, PhD; Haiying Chen, MD, PhD; Debbie Golden, BS; Edison Floyd, BS; and Susan E. Appt, DVM.
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 (e.g., cross-sectional and uncontrolled investigational studies).
Level III  Meta-analyses; reports from expert committees; descriptive studies and case reports.

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