CLINICAL UPDATE

Update in Women's Health 2006–2007

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In this paper, we summarize recent women's health articles and guidelines that could potentially change practice, presented at the 30th annual meeting of the Society of General Internal Medicine.

METHODS

We limited our search to articles published between March 1, 2006 to February 28, 2007 in one of 10 publications: *ACP Journal Club*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, *JAMA*, *Journal of General Internal Medicine*, *Journal of Women's Health and Gender-Based Medicine*, *Lancet*, *New England Journal of Medicine*, *Obstetrics and Gynecology*, and *Women's Health Watch*. All study designs and populations were considered. We defined "women's health" broadly, including conditions of the female reproductive tract and breast, conditions that preferentially or differentially affect women (e.g., domestic violence, osteoporosis), and prevention and screening of these conditions. As our audience was general internists, we included medical conditions in pregnancy, but excluded surgical and obstetrical aspects of women's health. A team of academic faculty with clinical and research experience in women's health evaluated publications based on 4 factors: (1) the degree of impact on the practice of general internists, (2) the degree to which its content was generally known (we wished to include topics that the public might question their internists about), (3) the study quality, and (4) the degree of focus on women's health. Major articles are discussed here.

In addition, we reviewed guidelines published or highlighted in the 10 journals listed above. Guidelines were selected based on the same criteria for articles, in addition to the degree to which it recommended a change in current practice management (e.g., new or changed recommendation).

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RESULTS

With this strategy, we identified nearly 180 reports with potential relevance, of which 9 were selected for in-depth discussion. In addition, Table 1 presents the results of our review of guidelines with potential relevance for women's health.

SSRIs, SNRIs, Gabapentin, and Clonidine Modestly Effective for Reducing Hot Flashes

Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006; 295(17): 2057–71.

Since the publication of the Women's Health Initiative,^{1,2} concerns about the adverse effects of hormone therapy have led to an increased interest in alternatives to treat menopausal symptoms. The efficacy and adverse effects of these alternative therapies are uncertain.

To assess the efficacy and adverse events of nonhormonal therapies for hot flashes, authors conducted searches of MEDLINE, PsycINFO, Cochrane Database, MANTIS, and AMED for articles up to October 2005 to identify English-language, randomized, double-blind, placebo-controlled trials of nonhormonal therapies. Trials were included in the systematic review if hot flash frequency, severity, or a composite score (frequency × severity) was reported. Trials of women with breast cancer were included, and trials of dietary, herbal, and behavioral therapies were excluded. Authors conducted a meta-analysis for trials that reported adequate data on hot flash frequency, the most commonly reported outcome across trials.

Authors identified 43 trials that met criteria for review. Trials were rated on quality (i.e., good, fair, poor), and 24 were included in the metaanalysis (19 excluded because of poor quality or lack of accurate hot flash frequency data). The number of hot flashes per day decreased compared to placebo in the metaanalysis of 7 comparisons of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) (mean difference, 1.13 fewer per day), 4 trials of clonidine (0.95 fewer per day at 4 weeks, 1.63 at 8 weeks), and 2 trials of gabapentin (2.05 fewer per day). The frequency in hot flashes was not reduced for the metaanalysis of red clover, and results were mixed for soy isoflavone.

Although SSRIs/SNRIs, clonidine, and gabapentin reduced hot flash frequency, the efficacy was less than reported for estrogen (2.5–3 fewer hot flashes per day).³ Whereas some studies supported a reduction in the severity of hot flashes or composite score with these alternatives, this was not includ-

Table 1. Important Women's Health Updated or New Guidelines in 2006-2007

Guideline Topic	Organization	Main Comments or Updated Recommendations
Abnormal Cervical Cytology in Adolescents ¹⁴	ACOG	Given the rarity of cervical cancer in women younger than 21 years, adolescents should undergo their first Pap test within 3 years after the onset of vaginal intercourse and no later than age 21 years. Aggressive management of benign lesions (i.e., LSIL, CIN 1 or 2) in adolescents should be avoided as these lesions have high rates of regression (50–70%); instead, such patients should have close follow-up with repeat cytology at 6 and 12 months for LSIL or CIN1, and repeat cytology or colposcopy at 4–6 months for CIN 2.
Evidence-based Guidelines for CVD Prevention in Women ¹⁵	AHA and others	CVD prevention is important in all women, as average lifetime risk is very high (approximately 1 in 2). CVD risk assessment therefore places greater emphasis on lifetime rather than on short-term absolute risk (i.e., Framingham risk score). Preventive therapy should include aspirin (75–325 mg) therapy for all women at high risk. Aspirin (81–100 mg) therapy should also be considered women older than 65 years to prevent stroke and MI if blood pressure is well controlled and benefits outweigh the risks, and in women younger than 65 years when benefit for ischemic stroke prevention is likely to outweigh adverse effects. However, aspirin use is not recommended to prevent MI in women <65 years of age. Hormone therapy, SERMs, antioxidant vitamins, and folic acid should not be used for primary or secondary prevention of CVD.
Hormonal Contraception in Women with Coexisting Medical Conditions ¹⁶	ACOG	Progestin-only methods of contraception may be safer than combined hormonal contraception in women with migraines (especially those with focal neurologic signs); cigarette smoking or obesity in women >35 years; history of VTE; hypertension in women >35 years or with vascular disease; SLE with vascular disease, nephritis, or antiphospholipid antibodies; less than 3 weeks postpartum; hypertriglyceridemia; CAD; CHF; cerebrovascular disease. Healthy, nonsmoking women who tolerate combined contraceptives may continue with that method until the ages of 50–55 years.
HPV Vaccine ¹⁷	CDC and ACIP	FDA-approved in June 2006 for ages 9–26, this 3-part series (0, 2, and 6 months) is currently recommended as a routine immunization for girls ages 11–12 and catch-up immunization for women up to age 26. 100% effective in preventing precancerous lesions and genital warts due to HPV 6, 11, 16, and 18. HPV 16 and 18 cause about 70% of all cervical cancers.
STD Treatment Guidelines ¹⁸	CDC	Gonorrhea: quinolone-resistant <i>N. gonorrhea</i> is increasing in the U.S. and are no longer recommended for treatment in California or Hawaii, or for infections acquired during foreign travel. Notify local health departments of cases in which quinolones have failed; such patients should be recultured for susceptibility tested. Trichomoniasis: Tinidazole is now recommended as a treatment option for non-pregnant women. Genital Herpes: Treatment options for recurrences now include 2 shortened regimens: 1-day famciclovir (1,000 mg bid) or 2-day acyclovir (800 mg tid). Suppressive therapy also appropriate in patients with infrequent outbreaks, as valacyclovir decreases HSV-2 transmission in discordant, heterosexual partners. Chlamydia trachomatis: Clinical experience and several studies now suggest that azithromycin is safe and effective in pregnant women.
Vaginitis ¹⁹	ACOG	Treatment of vulvovaginal candidiasis: In severe cases, a second dose of fluconazole 150 mg given 3 days after first dose increases cure rate from 67% to 80%. Recurrent cases may be treated with prolonged antifungal treatment: fluconazole 150 mg weekly for 6 months, after initial intensive treatment for 7–14 days to achieve mycologic remission; found to successfully suppress more than 90% of symptomatic episodes. Prolonged maintenance with intermittent topical agents, e.g., clotrimazole 500 mg weekly or 200 mg twice weekly, are acceptable for suppression. Diagnosis of vaginitis: Microscopy is considered first line for establishing a diagnosis. Culture and other point-of-care testing should be considered if the diagnosis is not proven by microscopy or a microscope is not available: culture or trichomonas rapid antigen testing for trichomoniasis, fungal culture for vulvovaginal candidiasis, pH and amines, and vaginal sialidases on vaginal specimens for bacterial vaginosis.

ACIP=Advisory Committee on Immunization Practices, ACOG =American College of Obstetrics and Gynecology, AHA=American Heart Association, CAD=coronary artery disease, CDC=Centers for Disease Control, CHF=congestive heart failure, CIN=cervical intraepithelial neoplasia, CVD=cardiovascular disease, FDA=Food and Drug Administration, HPV=human papillomavirus, HSV=herpes simplex virus, LSIL=low-grade squamous intraepithelial lesion, MI=myocardial infarction, SERM=selective estrogen-receptor modulator, SLE=systemic lupus erythematosus, STD=sexually transmitted infection, VTE=venous thromboembolism

ed in the metaanalysis. This study was limited by the weaknesses of many of the trials, such as small study populations, short-term follow-up, and methodological flaws. Other limitations include potential publication bias and exclusion of non-English publications.

Conclusions. In women who cannot or prefer not to take hormone therapy, SSRIs/SNRIs, clonidine, and gabapentin are reasonable options. Although there are no head-to-head studies, the data for venlafaxine⁴ (in breast cancer survivors) and paroxetine⁵ (in a general population of women) suggest

that they may be more effective than other SSRIs. Gabapentin or clonidine may be preferred over SSRIs in women taking tamoxifen, which may interact with SSRIs.⁶

Black Cohosh Not Effective for Vasomotor Symptoms in Well-Designed Trial

Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh multibotanicals, soy, hormone therapy, or placebo. *Annals of Internal Medicine* 2006;145: 869–79.

Black cohosh is one of the most commonly used alternative therapies to treat vasomotor symptoms. Previous studies of black cohosh have been small, short trials (<12 weeks) with mixed results.⁷

In this 1-year randomized, double-blind, placebo-controlled trial (HALT study=Herbal Alternatives for Menopause Trial), 351 peri- or postmenopausal women age 45–55 with at least 2 vasomotor symptoms per day were randomized to 1 of 5 interventions: (1) black cohosh 160 mg/day ($n=80$), (2) multibotanical with black cohosh 200 mg/day and 9 other ingredients ($n=76$), (3) multibotanical + dietary soy counseling ($n=79$), (4) CEE 0.625 mg/day $\pm$ medroxyprogesterone acetate 2.5 mg/day ($n=32$), or 5) placebo ($n=84$). Women with history of breast cancer were excluded. Outcomes were changed in frequency and severity of hot flashes at 3, 6, and 12 months and Wiklund Vasomotor Symptom Scale scores.

Ninety-two percent of women finished the study, and 87% were taking study medication at 12 months. The placebo group experienced an approximate 30% reduction in symptom frequency and severity over the course of 1 year. There were no differences between the herbal interventions and placebo at 3, 6, or 12 months with one exception: the multibotanical + dietary soy group had higher severity scores at 12 months compared to placebo ($p=0.02$). The hormone therapy (HT) group averaged 4 fewer vasomotor symptoms per day compared to placebo ($p<.001$) and Wiklund scores were significantly lower at all time points ($p<.001$). There were no differences in adverse effects between the groups except breast tenderness and menstrual disorders were more common in the HT group.

Conclusion. This study provides strong evidence that black cohosh alone or as part of a multibotanical treatment is not effective for vasomotor symptoms. The “placebo effect” in HALT is consistent with prior studies. Whether this is actually the natural progression of menopause or caused by other self-care treatments is unknown, but women experiencing hot flashes can be reassured that they are likely to have fewer symptoms over the next 12 months.

Adding/Switching to a Second Agent are Acceptable Approaches to Initial SSRI Failure

Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006;354(12):1231–42.

Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006;352(12):1243–52.

Major depressive disorder is common among women, and selective serotonin reuptake inhibitors (SSRIs) are often used as first-line therapy. Second-step approaches include augmentation with a second agent or switching to another agent.

In these two randomized, multicenter trials from the STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) conducted in the United States, 4,177 adults (59% women) diagnosed with nonpsychotic major depressive disorder received the SSRI citalopram as initial therapy. Participants who either did not have a remission or could not tolerate citalopram after up to 14 weeks of therapy were either switched to another regimen or were given a second drug as augmentation to the citalopram. In the study by Rush et al., 727 participants were randomized to be switched to either bupropion-SR, sertraline, or extended release venlafaxine. In the study by Trivedi et al., 565 participants were randomized to receive bupropion-SR or buspirone as augmentation to citalopram. The primary outcome was symptom remission, defined by the Hamilton Rating Scale for Depression at the end of the study.

Remission rates for the switch groups did not differ significantly (21%, 18%, and 25%, respectively; $p<.16$), and there were no differences in adverse events. Remission rates for bupropion-SR and buspirone augmentation did not differ significantly (30% for both), but participants taking bupropion-SR had lower symptom scores (by the Quick Inventory of Depressive Symptomatology—Self Report; $p<.02$) and fewer discontinuations because of intolerance (13% vs 21%; $p<.001$).

These trials had several limitations. Patients could opt out of certain second-step therapies and were not blinded to treatment (although outcomes were collected by blinded investigators). Few patients agreed to either switch or augmentation, preventing a direct comparison of switch versus augmentation strategies. Further, cognitive therapy was not included as part of the treatment.

Conclusions. Changing to another antidepressant (bupropion-SR, SNRI, or another SSRI) or adding a second agent is an acceptable approach to initial SSRI failure. Intolerance or failure to one SSRI may not predict lack of tolerance or efficacy with another SSRI. Augmentation with bupropion-SR may be preferred over augmentation with buspirone because of better tolerance and symptom reduction.

Self-Reported Methods of Domestic Violence Screening Preferred by Women

MacMillan HL, Wathen CN, Jamieson E, et al. Approaches to screening for intimate partner violence in health care settings. *JAMA* 2006; 296:530–536.

Domestic violence (DV) is common in all socioeconomic groups and increases the risk of future injury and death. It is recommended that women be screened for DV although there is limited data on the screening method preferences of patients and the effectiveness of brief screening tools.

In this study, 2,461 English-speaking women between the ages of 18 and 64 were recruited from family practices, emergency departments (EDs), and women's health clinics in Canada. The participants were randomized to one of 3 screening methods (computer, written, or face-to-face) using 2 screening instruments, the Women Abuse Screening Tool

(WAST, 8 items) and the Partner Violence Screen (PVS, 3 items). Participants also completed the Composite Abuse Scale (CAS, a 30-item validated research instrument as gold standard.) Participants rated each instrument using 3 questions, each on a 5-point ordinal scale: 1. "Was it easy?" 2. "Did you like answering it?" and 3. "Was it private enough?"

The 12-month prevalence of intimate partner violence (IPV) ranged between 4.1% and 17.7% and depended on method, instrument, and setting. The sensitivities and specificities of the PVS (49.2% and 93.7%, respectively) and WAST (47.0% and 95.6%, respectively) were similar when using the CAS as gold standard. Women who were randomized to computerized and written methods of screening were more likely to give those methods the highest rating of 5 compared to women randomized to the face-to-face method.

Limitations of this study include no accounting for the length of the patient-provider relationship, given that a woman may be more likely to disclose to a provider with whom they have had an ongoing relationship. Further, only English-speaking women were enrolled in this study.

Conclusions. Most women prefer self-reported methods of DV screening, such as computerized or written. Both the WAST and PVS screening tools (whose questions are available in their entirety in the JAMA article) are brief screening instruments that can be easily used in clinical settings.

Migraine With Aura Associated with Increased Risk of Cardiovascular Events

Kurth T, Gaziano JM, Cook NR, et al. Migraine and risk of cardiovascular disease in women. *JAMA* 2006; 296:283-91.

Previous research has suggested that migraine with aura is associated with an increased risk of stroke, but its association with coronary artery disease is unclear.

The authors used data from 27,840 women, 45 years or older and free of cardiovascular disease or angina, enrolled in the Women's Health Study. Participants completed a mailed survey at baseline reporting information about cardiovascular risk factors and migraine assessment. Follow-up surveys were mailed yearly for 10 years and included questions regarding cardiovascular events, coronary revascularization, and angina. Outcomes were confirmed by medical record review. Participant follow-up was 97.2% complete, and mortality data was 99.4% complete.

The prevalence of migraine in the study population was 18.4%. Of 3,610 women with active migraine (within the preceding year at baseline), 1,434 (39.7%) reported aura. Women with migraine without aura had no increased risk for any cardiovascular events. Migraine with aura status was

associated with a significantly increased risk of major cardiovascular events after adjustment for a large number of cardiovascular risk factors (Table 2).

Limitations of this study include that migraine and aura status were self-reported, no information about the use of migraine-specific drugs was obtained, and the population was primarily older white women.

Conclusions. Migraine with aura may identify women at increased risk of atherosclerotic disease.

Extensive Mammographic Density is a Risk Factor for Developing Breast Cancer

Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007;356:227-36.

Prior literature suggests an increased risk of breast cancer among women with extensive mammographic density. The extent to which this is caused by poorer mammogram sensitivity (masking) among those with greater density is unclear.

A nested case-control study was conducted using data from three different mammographic screening programs in Canada. In total, 1,112 breast cancer cases were matched to 1,112 controls based on age, year of entry into the screening program, and by screening center. The percentage of mammographic density was assessed for the case subject's unaffected breast and the corresponding breast of the control.

After adjustment for other breast cancer risk factors, the odds ratio (OR) for developing cancer for women with at least 75% density was 4.7 (95% CI, 3.0-7.4), compared to those with less than 10% mammographic density (Table 3). These findings are consistent with another article published in 2006 that found women with breasts rated as heterogeneously or extremely dense had an odds ratio of about 3 for developing breast cancer.⁸

The study by Boyd supports the hypothesis that some masking occurs, with the high odds ratio for finding cancer less than 12 months after a negative screening exam. However, this study also supports a biologic association between mammographic density and breast cancer incidence, given the persistently high odds ratios over an 8-year follow-up duration.

Given the fact that breast density can now be considered a risk factor for breast cancer, what strategies can be used in the approximately 25% of patients who have this risk factor? It is possible that an alternative screening method (i.e., breast MR or ultrasound) would be more sensitive for finding breast cancer in women with dense

Table 2. Multivariable-Adjusted Hazard Ratios (95% CI) for Ischemic Vascular Events According to Migraine Status

Outcomes	No Migraine History (N=22,715)	Active Migraine with Aura (N=1,434)	Active Migraine Without Aura (N=2,176)	Prior Migraine (N=515)
Major Cardiovascular Event	1.0	2.15 (1.58-2.92)	1.23 (0.88-1.73)	1.14 (0.82-1.58)
Ischemic Stroke	1.0	1.91 (1.17-3.10)	1.27 (0.77-2.09)	0.77 (0.43-1.38)
Myocardial Infarction	1.0	2.08 (1.30-3.31)	1.22 (0.73-2.05)	1.14 (0.69-1.88)
Death Due to Cardiovascular Event	1.0	2.33 (1.21-4.51)	1.06 (0.46-2.45)	1.65 (0.90-3.01)

CI=confidence interval

Table 3. Odds Ratios (95% CI) for Mammographic Density and Risk of Breast Cancer

Density	All	Screening Detected	Detected < 12 Months After Negative Screening	Detected > 12 Months After Negative Screening
<10%	1.0	1.0	1.0	1.0
10 to <25%	1.8 (1.4–2.2)	1.6 (1.2–2.2)	2.1 (0.9–5.2)	2.0 (1.2–3.4)
25 to <50%	2.1 (1.6–2.6)	1.8 (1.3–2.4)	3.6 (1.5–8.7)	2.6 (1.5–4.6)
50 to <75%	2.4 (1.8–3.3)	2.0 (1.3–2.9)	5.6 (2.1–15.3)	3.1 (1.6–6.2)
≥75%	4.7 (3.0–7.4)	3.5 (2.0–6.2)	17.8 (4.8–65.9)	5.7 (2.1–15.5)

CI=confidence interval

breasts. However, there are no direct data to speak to this, nor to permit estimation of the positive predictive value. Because of the masking effect, it would seem unlikely that shortening the interval between routine mammograms will be a particularly useful strategy. Combined with the traditional breast cancer risk factors, this risk factor may help identify women who could appropriately consider chemoprevention with tamoxifen or raloxifene.

Chemoprevention for Breast Cancer is Effective, but Both Agents Studied Have Substantial Adverse Effect Profiles

Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women (RUTH Trial.) *N Engl J Med* 2006;355:125–37.

Raloxifene is a selective estrogen-receptor modulator (SERM) presently FDA-approved for osteoporosis therapy. Prior studies have shown potential beneficial effects on the incidence of breast cancer and coronary heart disease.

The investigators of the RUTH Trial conducted a multicenter, double-blind, placebo-controlled randomized trial of raloxifene at 60 mg daily for a median follow-up of 5.6 years. Subjects were 10,101 postmenopausal women with coronary heart disease (CHD) or CHD risk factors; 41% were at elevated risk of breast cancer.

Despite modest improvement in lipid profiles, raloxifene had no effect on the risk of CHD events, or on overall or cardiovascular mortality. Raloxifene decreased the risk of invasive breast cancer substantially (HR 0.56, 95% CI 0.38–0.83) without changing the risk of non-invasive breast cancer. This reduction was observed only among those with ER-positive breast cancer (HR 0.45, 95% CI 0.28–0.72). Raloxifene decreased clinical vertebral fractures (HR 0.65, 95% CI 0.47–0.89) without affecting other fractures. Women randomized to raloxifene had more venous thromboembolism, more fatal (but not overall) strokes, and more hot flushes, leg cramps, and peripheral edema.

Conclusion. Treatment with raloxifene reduces the incidence of breast cancer and vertebral fractures, but at a risk of thromboembolic disease and fatal stroke.

Two additional papers compared the effects of raloxifene with tamoxifen for breast cancer chemoprevention.

Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727–926.

Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2742–51.

To directly compare tamoxifen and raloxifene with respect to efficacy and adverse effects for breast cancer chemoprevention, a multicenter randomized controlled trial of 19,471 postmenopausal women aged 35 and older was conducted in the United States and Canada. Eligible women had a 5-year predicted breast cancer risk of $\geq 1.66\%$ based on the Gail model and had no history of stroke, thromboembolism, or certain other illnesses. Women were randomized to tamoxifen 20 mg daily or raloxifene 60 mg daily for 5 years.

There was no difference between the groups in the risk of invasive breast cancer (RR 1.02, 95% CI 0.82–1.28). Fewer non-invasive breast cancers occurred in the tamoxifen group ($p=0.052$). Although endometrial hyperplasia (RR 0.16, 95% CI 0.09–0.29) and hysterectomies (RR 0.44, 95% CI 0.35–0.56) were more common in the tamoxifen group, uterine cancer was similar for both groups. Raloxifene caused 30% fewer thromboembolic events, but there was no difference in ischemic heart disease, stroke, osteoporotic fractures, or death. There was no difference between raloxifene and tamoxifen groups in the MOS SF-36 physical or mental component summary scales or CES-D depression scale. Women treated with tamoxifen were more likely to remain sexually active (OR = 1.22, 95% CI 1.01–1.46) and reported less difficulty with sexual interest and enjoyment. With respect to symptoms, women treated with raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain. Women treated with tamoxifen experienced more cataracts, vasomotor symptoms, bladder problems, gynecologic problems, and leg cramps.

In summary, raloxifene and tamoxifen had similar efficacy for breast cancer chemoprevention but different side effect profiles. Either could reasonably be used in women at high risk of breast cancer.

The RUTH and STAR Trials provide important information for those contemplating offering chemoprevention to a given patient. Both raloxifene and tamoxifen reduce the incidence of invasive breast cancer similarly by about 45–50% over 5 years. The relative improvement is similar across demographic factors. Raloxifene may not reduce the risk of non-invasive breast cancer. The NSABP-P1 trial⁹ showed that tamoxifen does so by about 50% over 5 years. How important this is in the longer run is unknown.

With respect to weighing the absolute benefit of these drugs compared to the risks, the prior probability of breast cancer is very important. For example, in the RUTH study (women at lower breast cancer risk), the excess thromboembolic events

equaled the breast cancers averted. However, in the STAR study, the number of breast cancers likely averted was greater than the thromboembolic events likely caused for either drug. Before considering chemoprevention for a patient, the patient's predicted risk of developing breast cancer should be calculated to determine appropriateness of therapy and so that adequate counseling can be done. An easy way to do this is with the breast cancer risk calculator on the National Cancer Institute's website at: <http://www.cancer.gov/bcrisktool>.

Repeat Bone Density Does Not Improve Fracture Prediction in Some Older Women

Hillier TA, Stone KL, Bauer DC, et al. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women: The study of osteoporotic fractures. *Arch Intern Med* 2007;167:155–160.

There is little evidence regarding the most appropriate interval for repeat osteoporosis screening with dual x-ray absorptiometry (DXA) measurements of bone mineral density (BMD) among patients without osteoporosis.

This study of the utility of a second hip DXA test was performed using a previously reported cohort of patients who had now been followed for 15 years or more. Among these 4,124 women (average age 72 at enrollment in 1990, initial T-score -1.4), the independent contribution of a second DXA test approximately 8 years after a first test was assessed. The authors used logistic regression models and assessments of ROC curves adjusted for age and weight to assess the test's value in predicting total clinical nonspine fractures and morphometric spine fractures.

The authors found that change in BMD from a first to a second test approximately 8 years later independently predicted fractures (HR 1.29 [1.15–1.45] per standard deviation in BMD measurement). However, when compared with a curve including only initial BMD, the addition of a second BMD result did not improve the area under the curve (0.73 for model adjusted for first BMD test only, 0.74 for both initial BMD and change in BMD).

This study was limited by its cohort consisting only of white women, who also appeared to have initial bone density higher than average for their ages.

Conclusion. For patients who are not close to a treatment threshold on initial testing, repeat testing is not likely to change clinical decision-making. Patients with initial BMD tests close to treatment thresholds or on treatment might benefit from repeat testing.

After Completion of 5 Years of Alendronate, Overall Fracture Risk Reduction is Maintained for 5 Years Off Therapy

Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: The fracture intervention trial long-term extension (FLEX): A randomized trial. *JAMA* 2006; 296:2927–38.

Alendronate is estimated to have a half-life of 15 years.¹⁰ Among women who took alendronate for 5 years, BMD has previously been shown to decline gradually after its discontin-

uation.¹¹ The effect of continuing bisphosphonates beyond 5 years on fractures is unknown.

Women taking alendronate 10 mg daily for a mean of 5 years during and after a prior randomized controlled trial were invited to enroll. A total of 1,099 subjects were re-randomized to continue alendronate (5 or 10 mg) or take placebo. At baseline, the mean T-score at the total hip was -1.9 , and approximately 35% of subjects had vertebral deformities on x-ray. The study outcomes included changes in BMD and an intention-to-treat analysis was performed among the entire group with a post-hoc subgroup analysis by baseline BMD and baseline vertebral deformities.

Continuation of alendronate for 5 years in this study was found to maintain or increase bone mass at all sites, and reduce clinical vertebral fractures compared with discontinuation (2.4% vs 5.3% clinical vertebral fracture rate, for a NNT=40). Continuation did not significantly reduce the risk of total fractures (19.9% vs 21.3%, RR 0.93 [0.71–1.21]) or x-ray-detected vertebral fractures (9.8% vs 11.3%, RR 0.86 [0.60–1.22]) over the next 5 years. The absolute risk for total fracture among those in the placebo group with a baseline BMD of ≤ -2.5 was high at 29.5% and fell to 22.6% among treated patients, although this difference was not significant. There were no differences in the fracture outcomes by subgroup.

This study had limited power to detect differences in fractures, as seen in the wide confidence intervals and the authors' reported power estimates. Nonetheless, the study had yearly fracture rates similar to those in earlier trials, and the BMD results showing gradual decrease in BMD to near pre-alendronate baseline at 5 years are consistent with the fracture results. Although there are no studies comparing discontinuation of different medications directly, BMD appears to drop more gradually after alendronate use than after estrogen, raloxifene, or teriparatide.

Conclusion. Patients can be counseled that if alendronate is discontinued after 5 years of use, fracture benefits still continue for at least 5 additional years. High-risk patients with T-scores below -2.5 or vertebral fractures at 5 years have larger absolute risk reductions with continuing alendronate and should probably continue bisphosphonate therapy.

Osteonecrosis of the Jaw Probably Rare with Oral Bisphosphonates

Woo S, Hellstein JW, Kalmar JR. Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws. *Ann Intern Med* 2006;144:753–61.

In 2004, the first reports of osteonecrosis of the jaw (ONJ) associated with aminobisphosphonates (alendronate, risedronate, pamidronate, zoledronic acid, and ibandronate) were published. There is no universally accepted definition of ONJ, but it typically appears as an area of exposed alveolar bone in the mandible or the maxilla. ONJ prevalence and factors associated with its development have not been well-described.

This systematic review examined all reports (all were case series or case reports) of ONJ and bisphosphonates used for any indication. They summarized the results of 368 cases published by January 2006 and found that about one-third of the cases were painless and 60% were preceded by a dental procedure. Over 96% of cases occurred in patients receiving

intravenous (IV) bisphosphonates, nearly all for cancer or diseases other than osteoporosis. The authors identified 15 reports of ONJ in patients being treated with oral bisphosphonates for osteoporosis.

The study was limited by the poor quality of the studies, which limited the authors' ability to do a quantitative meta-analysis. However, the qualitative review suggests that among cancer patients, the prevalence of ONJ may be as high as 10%. The prevalence of ONJ among patients who use oral bisphosphonates for osteoporosis could not be estimated from this review or any current studies.

Conclusion. Even with a few reports subsequent to this review,¹² users of oral bisphosphonates for osteoporosis appear to be at very low risk of ONJ. Based on an estimated 15–20 million person-years of experience with oral bisphosphonate use by the end of 2003,¹³ the risk among osteoporosis patients is probably less than 1/100,000 patient-years.

Conflict of Interest: None disclosed.

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