CLINICAL UPDATE

Update in Women's Health

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KEY WORDS: women's health; breast cancer; osteoporosis; menopause; contraception.

DOI: 10.1007/s11606-006-0066-3

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Women's health occupies much of the General Internist's ambulatory practice. We sought to summarize recent women's health articles and reports that could potentially change practice. We defined "women's health" broadly, including symptoms and conditions of the female reproductive tract and breast, conditions that preferentially or differentially affect women in a significant way (such as osteoporosis or heart disease in women using postmenopausal hormones), and prevention and screening of these conditions. We excluded surgical and obstetrical aspects but included medical conditions of pregnancy.

This update was presented at the 29th annual session of the Society of General Internal Medicine, and the search strategy thus focused on publications from April 1, 2005 to February 28, 2006. Because the topic area was broad, the time period short, and the goal to identify important reports, the initial method of locating potential articles was the review of 10 pertinent journals (*ACP Journal Club*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, *JAMA: the Journal of the American Medical Association*, *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.

With this strategy, we identified nearly 200 articles and Federal Drug Administration (FDA) advisories with potential relevance. In conferences, a team of academics with clinical and research experience in women's health discussed each item, delineating the degree of impact on the practice of General Internists, the degree to which its content was generally known (we wished to include articles that the public might question their Internists about), the study quality, and the degree of focus on women's health. Major reports are discussed here; minor reports are tabulated in the [Appendix](#). A summary of relevant guidelines is in [Table 1](#). A summary of practice changes stemming from the articles reviewed here is in [Table 2](#).

Received July 27, 2006

Accepted November 10, 2006

Published online June 5 2007

Contraceptive Patch Has Higher Total Estrogen Exposure than Oral Contraceptives

van den Heuvel MW, van Bragt AJM, Alnabawy AKM, Kaptein MCJ. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005;72:168–74.

Transdermal administration of estradiol eliminates first-pass hepatic metabolism and may theoretically reduce the risk of venous thromboembolism (VTE) associated with oral estrogen. A small, open-label randomized trial was conducted to compare the pharmacokinetics of ethinyl estradiol (EE) when administered in one of three ways: (1) the vaginal ring (Nuvaring, 15 mcg EE), (2) the transdermal patch (OrthoEvra, 20 mcg EE), or (3) a combination oral contraceptives (OCs) (Leven, 30 mcg EE). The participants were 24 healthy, nonobese women (mean age 23, 25, or 26, depending on group assignment). They received one of the three preparations for 21 days.

The total exposure to EE (defined as the area under the curve) in the patch group was 3.4 times higher than the ring group and 1.6 times higher than the OC group ($P < .05$ for both comparisons). The peak EE exposure in the OC group was 4.5 times higher than the ring group and 1.6 times higher than the OC group ($P < .05$ for both comparisons). Individual variations in serum EE levels were greatest in the patch group while day-to-day variations were greatest in the OC group.

The study was limited by its small size and was not powered for major or minor adverse events. Several authors were employed by the ring manufacturer. Obese women were not included because it is known that the patch is less effective in obese patients.

In response to these findings, the FDA updated the OrthoEvra contraceptive patch labeling to warn that the patch exposes women to 60% more total estrogen than typical OCs.¹ It is unknown if higher estrogen exposure translates into greater clinical risks and whether total exposure is a better marker for risk than peak exposure. A recent study² did suggest a slight, but not statistically significant, increased nonfatal VTE risk for the patch compared to a 35-mcg EE/norgestimate OC (5.3 vs 4.2 events per 10,000 women-years, $P > .05$); note that the risk is about 1 per 10,000 in nonusers).

The potential risks of hormonal contraception must be balanced with the potential risks of pregnancy. Compliance with the weekly patch may be better than with a daily OC;

Table 1. Important women's health guidelines in 2005–2006

Guideline topic (reference)	Organization	Main recommendations or conclusions and comments
Emergency contraception	ACOG	Emergency contraception should be made available to all women who had unprotected (or inadequately protected) sexual intercourse and who do not desire pregnancy. Emergency contraception prescriptions and options, concomitant antinausea medications, efficacy, and follow-up are discussed.
Abnormal cervical cytology	ACOG	Women with atypical squamous cells can be followed with immediate colonoscopy, high-risk DNA HPV testing, or repeat Pap at 6 and 12 mo. Women with positive high-risk HPV need colonoscopy; if this is low-risk, Pap may be repeated in 6 and 12 mo or simply repeat HPV in 12 mo. Women with negative low-risk HPV may have Pap repeated in 12 mo. Natural history, test sensitivity and specificity, and other recommendations are discussed.
Breast cancer genetic mutation screening	USPSTF	Women with an increased risk pattern for breast or ovarian cancer in their family history should be referred for genetic counseling and evaluation of BRCA mutations. Increased risk patterns include (1) 2 first-degree relatives if 1 was aged 50 or younger at diagnosis; (2) 3 or more first- or second-degree relatives; (3) family history of both breast and ovarian cancer in first- or second-degree relatives; (4) 1 first-degree relative with bilateral breast cancer; (5) 2 or more first- or second-degree relatives with ovarian cancer; (6) breast cancer in a male relative; and (7) if Ashkenazi Jewish heritage, any first-degree relative or 2 second-degree relatives on the same side of the family with breast or ovarian cancer. Insufficient evidence exists to make recommendations on chemoprevention or intensive screening. There is fair evidence that prophylactic surgery significantly reduces breast and ovarian cancer incidence, with small magnitude of harm.
Menopausal transition	NIH Consensus Panel	Many women proceed through menopause without symptoms, but surgical menopause increases the risk of symptoms. Symptoms are primarily vasomotor and estrogen is the best treatment. Other topics are discussed: symptoms attributable to menopause, risk factors for and quality of symptoms, benefits and harms of treatments, and directions of future research.
Low sexual desire	North American Menopause Society (NAMS)	Postmenopausal women with decreased sexual desire causing personal distress may be candidates for testosterone therapy. Testosterone treatment without concomitant estrogen therapy cannot be recommended because of lack of evidence. Factors in sexual dysfunction, monitoring for efficacy and adverse effects, and custom-compounded products are discussed.

USPSTF=U.S. Preventive Services Task Force, ACOG=American College of Obstetrics and Gynecology, NIH=National Institutes of Health

alternatives include injectables, ring, IUD, and sterilization. Patients with VTE or cardiovascular risk factors should be counseled about alternatives to patch contraception.

FDA Advisory: Paroxetine Increases Risk of Fetal Heart Defects

U.S. Food and Drug Administration. Public health advisory: Paroxetine. Available at: <http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm>.

Depression is a common problem, particularly in reproductive-age women where the estimated prevalence is 10–20%. Frequently, serotonin reuptake inhibitors (SRIs) are used to treat depression, although their safety in pregnancy is uncertain. The FDA, because of safety concerns with first-trimester use of one SRI, Paxil (paroxetine), asked the manufacturer to investigate paroxetine's association with fetal anomalies.

The manufacturer submitted two studies: one using a Swedish national registry (including more than 6,800 women) and one using a U.S. insurance claims database (including more than 5,900 women).³ In the Swedish study, women who received paroxetine in early pregnancy had increased risk of having an infant with a cardiac defect compared to the entire registry population (2% of paroxetine-exposed infants had defects vs 1% of all infants, odds ratio [OR] 1.8, 95% confidence interval [CI] 1.1–2.8). In the U.S. study, women who received paroxetine in the first trimester had a nonsignificant increased risk of having an infant with cardiac malformations (OR 1.5, 95% CI 0.8–2.9) and an increased risk of having an infant with any congenital malfor-

mation (OR 1.8, 95% CI 1.2–2.8) compared to women who received *other antidepressants* in the first trimester. Most of the cardiac defects were atrial or ventricular septal defects.

As manufacturer reports, these data are not published in a peer-reviewed journal. Studies conducted by the manufacturer may be theoretically biased by a manufacturer's motivation to present its product in a positive light. However, in this case, these reports were requested by the FDA and the main finding was significant harm with the product.

The FDA has changed the pregnancy category of paroxetine from C (safety uncertain) to D (evidence of harm). Thus, any woman at risk for pregnancy should not be given paroxetine. Other antidepressants may be prescribed after a discussion of risks and benefits; competing SRIs and bupropion generally are pregnancy category C. Mild depression may be treated with cognitive or behavioral therapy. Women on an SRI who are pregnant or planning pregnancy should be evaluated for SRI discontinuation and counseled about depression relapse. Depression relapse is more frequent in women discontinuing antidepressants early in pregnancy than in women continuing them (68% vs 26%)⁴ (see article summary in the [Appendix](#)). In some patients, especially women with highly recurrent depression or depression of long duration, the benefits of continuing an antidepressant may be greater than the risk to the fetus (untreated depression can also lead to poor pregnancy and infant outcomes).

Women on an SRI during their third trimester should be also counseled about effects of late SRI use, including a low risk of neonatal pulmonary hypertension and infant behavioral problems^{5,6} (see article summaries in the [Appendix](#)). These risks must be balanced with benefits: third-trimester antidepressants may prevent postpartum depression and neonatal well-being depends on a mother free of depression.

Table 2. Summary of Changes in Women's Health Practice Stemming from Important 2005–2006 Reports

Practice Change
Do
Screen women for colorectal cancer with colonoscopy rather than flexible sigmoidoscopy when colonoscopy is available
Advise women concerned about their breast cancer risk to maintain a normal weight, rather than follow a low-fat diet
Discriminate between the risks and benefits of postmenopausal estrogen and the risks and benefits of postmenopausal estrogen plus progestin
Use gel lubrication if any discomfort is anticipated during a vaginal speculum examination, even if collecting Pap or chlamydia specimens
Vaccinate women and girls aged 9–26 against HPV
Encourage women with menopausal symptoms to try any management strategy (dietary, behavioral, nonprescription, or clinical) that resonates
Don't
Prescribe the contraceptive patch when venous thromboembolism or cardiovascular risk factors exist
Prescribe paroxetine to women of child-bearing age
Routinely supplement calcium intake above 1,200 mg/d in postmenopausal women
Consider
Supplementing vitamin D intake to 700–800 IU/d, especially in men and women at high risk for osteoporotic fracture
Prescribing testosterone to surgically menopausal women who are taking estrogen and have bothersome low libido, and then monitoring for adverse effects
Monitoring prothrombin time in women on chronic warfarin when prescribing single dose fluconazole
Prescribing parathyroid hormone for 1 year in persistently osteopenic women despite bisphosphonate therapy
Screening women over age 70 for subclinical hypothyroidism
Prescribing gabapentin 300 mg tid to breast cancer survivors who have menopausal vasomotor symptoms

SRI = serotonin reuptake inhibitor
“See article summaries in the [Appendix](#).

Colonoscopy Has Better Yield Over Flexible Sigmoidoscopy for Colorectal Cancer Screening in Women Compared to Men

Schoenfeld P, Cash B, Flood A, Dobhan, Eastone J, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med*. 2005;352:2061–8.

Both flexible sigmoidoscopy and colonoscopy are supported as colorectal cancer (CRC) screening options, but the availability of colonoscopy is limited. Some have suggested, because women have lower age-adjusted CRC rates, that flexible sigmoidoscopy is a reasonable alternative for CRC screening in women.

Women were recruited from military centers for two groups: average risk and higher risk. More than 1,400 women were enrolled; about 1,200 were on average risk, asymptomatic women, aged 50–79, who were referred for CRC screening; and 200 were asymptomatic women, aged 40–79, with a first-degree relative with colon cancer (“family history group”). Men

from a VA cooperative study were age- and risk factor-matched to enrolled women. All underwent colonoscopy only, and lesions in the rectum and sigmoid were defined as “within reach of flexible sigmoidoscopy”.

About 5% of average-risk women and 7% of family history women had advanced neoplasia, defined as adenomas ≥ 1 cm, villous adenomas, high-grade dysplasia, or invasive cancer. Among average-risk women, flexible sigmoidoscopy alone would have found advanced neoplasia in 1.7% but missed it in 3.2%. If colonoscopy were the gold standard, flexible sigmoidoscopy would have a similar sensitivity in detecting advanced neoplasia in both risk groups (30–35%).

In the 50- to 69-year-old age group, men were more likely to have advanced neoplasia than women, 8.6% versus 4.5% ($P = .002$). If the clinical strategy was to perform a colonoscopy if any size adenoma was found on flexible sigmoidoscopy, then 35% of advanced neoplasia would be found among women, compared to 66% among men.

Flexible sigmoidoscopies were not actually performed on the study participants (the colonoscopic findings were used as a surrogate), but a gender-based bias is unlikely. In addition, military populations lessen generalizability.

In conclusion, compared to men, women have a lower percentage of *distal* neoplasia. Thus, despite the lower prevalence of advanced neoplasia in women compared to men, flexible sigmoidoscopy would miss substantial absolute numbers of neoplastic lesions in both genders. Thus, if both are available, it appears difficult to recommend flexible sigmoidoscopy over colonoscopy for women.

A Low-Fat Diet Did Not Prevent Breast Cancer
Prentice RL, Caan B, Chlebowski R, Patterson R, Kuller LH, et al. Low-fat dietary pattern and risk of invasive breast cancer. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:629–42.

It is hypothesized that low intake of dietary fat leads to low estrogen levels, which decrease breast cancer risk. Indeed, diets high in fat are linked to increased breast cancer incidence in some ecologic studies, but other studies are conflicting. Observational studies examining effects of diet are often limited by measurement and recall biases. The Women's Health Initiative (WHI) directly assessed the benefits and risks of a low-fat diet in a randomized controlled trial (RCT). Its primary outcomes were breast and CRC⁷ (see article summary in the [Appendix](#)). A secondary cancer outcome was coronary heart disease (CHD)⁸ (see article summary in [Appendix](#)).

Eligible participants were healthy postmenopausal women, aged 50–79, without breast or CRC, who were consuming at least 32% of energy from fat at baseline. More than 48,000 were randomized asymmetrically because of cost: 40% to an intensive low-fat diet intervention and 60% to usual diet. Intervention diet goals were <20% energy from fat, 5 servings daily of fruits or

vegetables, 6 servings daily of grains, and weight maintenance. Intervention participants received customized fat goals, 18 group sessions in the first year, and quarterly sessions thereafter. Self-reports of breast cancer were confirmed by chart review.

At baseline, mean age was 62 and mean BMI was 29. Compared to the control group, the intervention group consumed 11% less calories from fat at year 1, and 8% less at year 6. At 1 year, the intervention women weighed 2.2 kg less; at 7.5 years, they weighed 0.4 kg less. Among a sample of 300 women, estradiol levels fell slightly more among intervention patients; estrone levels did not differ.

After a mean follow-up of 8.1 years, 655 (3.4%) of the women in the intervention group had developed breast cancer, compared to 1,072 (3.7%) women in the control group ($P=.07$; hazard ratio [HR] 0.91, 95% CI 0.83–1.01). Women with a higher fat consumption at baseline had a slightly greater reduction in breast cancer risk.

Women enrolled in the low-fat diet trial could participate in the other WHI trials (17% were in a hormone therapy trial and 50% were in the calcium + vitamin D trial); hormones are known to affect breast cancer risk, but did not appear to be a significant interaction in this analysis. Whereas the intervention group had lower fat intake than the control group, the trial is limited by the fact that relatively few women (31% at year 1, 14% at year 6) achieved the goal for dietary fat intake.

An intervention targeting fat stores instead of dietary fat intake may have been more effective. Among postmenopausal women, the main source of circulating estrogen is conversion of androgens to estrogens by aromatase in the adipose tissue. Thus, body stores of adipose tissue may be more important than fat intake. Based on this study and other literature relating postmenopausal obesity to breast cancer, it is reasonable to advise women concerned about their breast cancer risk to maintain a normal weight, rather than follow a low-fat diet.

Baseline intake was about 1,100 mg/day of calcium and 360 IU/day of vitamin D in both groups. There was no difference between groups in the risk of hip, vertebral, wrist, or total fractures (hip HR 0.88, 95% CI 0.72–1.08; vertebral HR 0.90, 95% CI 0.74–1.10). An increased risk in kidney stones was seen in the intervention group (HR 1.17; 95% CI 1.02–1.34). In a subgroup with dual x-ray absorptiometry measurements at 3, 6, and 9 years, there was a statistically significant reduction in bone loss at the hip ($P<.01$), but not at other sites.

The study was limited by a low rate of adherence to study medications: at the end of the trial, only 59% of the study participants were taking at least 80% of their assigned medication. Women in both groups were allowed to take personal calcium supplements. Because the baseline calcium and vitamin D intake was high, this study did not test supplementation among those with low baseline intakes. Finally, this study was underpowered for hip and vertebral fracture reduction (the fracture rate among control subjects was about half the expected rate).

This study does not offer a compelling reason to abandon the conventional strategy to supplement women to a daily calcium intake (dietary plus supplements) of 1,200 mg/day. There is insufficient evidence to supplement above 1,100 mg/day. Women should be counseled about a possible increased risk of kidney stones with calcium and vitamin D supplements at high levels. Other nonpharmacologic therapies (e.g., weight-bearing exercise and smoking cessation) should be discussed along with calcium supplementation. Other recent studies of calcium and vitamin D supplementation^{9,10} (see article summaries in the [Appendix](#)) had similar methodological problems and findings. However, a large meta-analysis¹¹ (see article summary in the [Appendix](#)) suggested calcium plus vitamin D modestly reduces risk of hip fractures, particularly in the frail, institutionalized elderly.

Calcium Supplementation Above 1,100 mg Not Helpful in Preventing Osteoporotic Fractures

Jackson RD, LaCroix AZ, Gass M, et al. Calcium and Vitamin D Supplementation and the Risk of Fractures. *N Engl J Med*. 2006;354(7):669–783.

Calcium supplementation is recommended to prevent osteoporosis and fractures, but previous trials have been small and conflicting. This study aimed to determine the efficacy of vitamin D and calcium in preventing hip and, secondarily, other fractures. It is a major constituent of the WHI series of trials.

More than 35,000 healthy postmenopausal women ages 50–79 were randomized to calcium carbonate 1,000 mg plus vitamin D 400 IU or placebo and were followed 7 years. About 50% were on hormone therapy. Self-reported fractures were confirmed by review of radiographs.

Higher Levels of Vitamin D Supplementation May Be Needed to Prevent Nonvertebral Fractures

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation. A meta-analysis of randomized controlled trials. *JAMA*. 2005;293(18):2257–64.

Vitamin D deficiency has been implicated in hip fractures, but the optimal supplementation dose is unknown. This study aimed to compare the risk of hip and other non-vertebral fractures with varying doses of vitamin D supplementation.

The authors performed a systematic meta-analysis of RCTs of vitamin D with or without calcium versus placebo. Seven RCTs were included, involving nearly 10,000 men and women over age 60 (mean 79 years); two thirds were

women. Five trials studied hip fractures: 3 employed 700 or 800 IU/day of vitamin D ($N=5,572$) and 2 employed 400 IU/day of vitamin D ($N=3,722$). Seven trials studied all nonvertebral fractures: 5 employed 700 or 800 IU/day of vitamin D ($N=6,098$) and 2 employed 400 IU/day of vitamin D ($N=3,722$).

Higher dose vitamin D supplementation (700–800 IU/day) reduced hip fracture risk (relative risk [RR] 0.74, 95% CI 0.61–0.88), whereas 400 IU/day did not (RR 1.15, 95% CI 0.88–1.50). Results were consistent in the ambulatory and institutionalized settings and between hip and nonvertebral fracture outcomes. The number needed to be treated with high-dose vitamin D supplementation was 45 persons to prevent 1 hip fracture and 27 to prevent 1 nonvertebral fracture.

Calcium supplementation was variable across trials: from no recommendation to dietary recommendation to supplements from 500 to 1,200 mg. Follow-up also varied, from 1 to 5 years. The majority of participants were white, which limits generalizability.

Vitamin D is inexpensive, easily available, and prevents nonvertebral fractures. All trials in this meta-analysis studied cholecalciferol (D3), rather than ergocalciferol (D2). To determine which form of vitamin D is in an over-the-counter supplement, read the ingredient list (not the supplement facts) on the bottle. Calcium supplementation is likely needed to prevent vertebral fractures¹¹ (see article summary in the [Appendix](#)). Adverse effects of long-term higher dose vitamin D are not known.

Estrogen Alone Does Not Increase Coronary Heart Disease Risk

Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease. *Arch Intern Med.* 2006;166:357–65.

Postmenopausal estrogen with progestin (E + P) increases CHD risk. The principal results of the WHI trial did not find a similar harm with estrogen alone. Hsia et al. presented a detailed analysis of CHD risk with estrogen alone.

Nearly 11,000 women aged 50–79 years with a history of a hysterectomy were randomized to 0.625 mg conjugated equine estrogens (CEE) or placebo for an average of 7 years (the trial was stopped early over concerns of stroke risk). Self-report of CHD outcomes were adjudicated. Very few participants had CHD at entry, but many had CHD risk factors (primarily hypertension).

Conjugated equine estrogen did not affect risk of CHD: about 0.5% of women per year had either coronary death or MI in both groups (HR 0.95, 95% CI 0.79–1.16). Whereas CHD history or risk factors did not affect the primary outcome, younger age (50–59 vs 60–79 years, $P=.07$) and lower C-reactive protein (<1.3 vs >1.3 mg/L, $P=.04$) trended toward

lower CHD risk. There was no statistically significant time trend, but risk decreased after 1–2 years.

This analysis is limited by the fact that it was underpowered to detect differences among age groups, but an adequately powered study would have required more than 17,000 women. In addition, fewer than half of all participants continued to take study medication at trial end.

Unlike E + P, estrogen alone appears not to confer CHD risk. The indications for estrogen use remain focused on menopausal symptoms. The decision to use estrogen in a symptomatic woman with a history of hysterectomy remains individualized and involves weighing risks (stroke, venous thromboembolic disease, cognitive impairment, and cholecystectomy) and benefits (menopausal symptom relief and osteoporotic fractures). C-reactive protein levels, duration of estrogen use, and a woman's age may alter risk–benefit profile. Estrogen with progestin confers more CHD risk than CEE alone ($P<.03$) and the risk–benefit profile differs (E + P increases the risk of breast cancer and decreases the risk of colon cancer).

Transdermal Testosterone Modestly Effective for Low Libido in Surgically Menopausal Women

Braunstein GD, Sundwall DA, Katz, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women. *Arch Intern Med.* 2005;165:1582–9.

Female sexual dysfunction is common: the community-dwelling prevalence is estimated at 25–63%. This study aimed to test the efficacy and safety of a testosterone patch for female hypoactive sexual desire disorder.

The multicenter RCT included surgically menopausal women with distressful low sexual desire on estrogen therapy. Eligible women were in a stable monogamous relationship with a sexually functioning partner. About 450 women (age 24–70 years, average age 50) were randomized to testosterone patches at the doses of 150, 300, or 450 mcg/day, or placebo for 24 weeks. Primary outcomes were changes in the sexual desire domain score (from a 7-domain questionnaire) and frequency of satisfying sexual activity (from weekly diaries of sexual activity).

There was no dose–response effect, but the 300-mcg/day dose resulted in small, statistically significant improvements in sexual desire scores. Compared to placebo, the absolute effect was about 7 points on a 100-point scale. The 300-mcg/day dose also increased the weekly number of satisfying episodes from 0.7 to 1.3, whereas placebo increased the weekly number of episodes from 0.7 to 1.0 ($P<.05$), yielding an absolute effect of about 1 more episode per month compared to placebo. Adverse effects were not significant. Total (but not

free) testosterone levels were above the normal reference range for all testosterone doses by week 12. Primary outcomes had a significant but small ($r=0.2$) correlation with free and total testosterone levels.

The trial was industry-sponsored and too short to assess long-term safety. Generalizability is limited in many ways. Results apply to a population taking considerable doses of estrogen (half were taking high-dose estrogen, i.e., >0.625 mg CEE), a population with self-described distressful low desire and yet 3 satisfying sexual episodes per month at baseline, and healthy surgically menopausal women. Also, conclusions about adverse lipid effects are limited to women with normal lipids.

This study targeted women with "female hypoactive sexual desire disorder." It is unclear how testosterone affects other sexual dysfunction disorders. The strong placebo effect highlights how simply discussing sexuality and diarying sexual episodes improves sexual well-being. Behavioral therapy should be tried first. Then consider lowering the estrogen dose (as vasomotor symptoms allow) because estrogen increases sex hormone binding globulin and thus decreases free testosterone. It is unclear whether testosterone is helpful in women with ovaries intact (who circulate ovarian testosterone) or in surgically menopausal women not taking estrogen.

The patch product is not available, so prescription of testosterone in women is limited to either oral combination of estrogen–testosterone (which may have more lipid effects than transdermal preparations that avoid the first-pass metabolism) or a modified dose of testosterone gel (FDA-approved only for men), such as a pea-sized portion of 1% gel. Any woman prescribed with testosterone should be monitored for adverse effects. Another transdermal testosterone trial reported a 10% increase in androgenic side effects such as acne, hirsutism, voice coarsening, and alopecia¹² (see article summary in the [Appendix](#)).

6. **Moses-Kolko EL, Bogen D, Perel J, et al.** Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA*. 2005;293(19):2372–83.
7. **Beresford SA, Johnson KC, Ritenbaugh C, et al.** Low-fat dietary pattern and risk of colorectal cancer. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:643–54.
8. **Howard BV, Van Horn L, Hsia J, et al.** Low-fat dietary pattern and risk of cardiovascular disease. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295: 655–66.
9. **Porthouse J, Cockayne S, King C, et al.** Randomized controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for the prevention of fractures in primary care. *Br Med J*. 2005;300: 1003–8.
10. **The Record Trial Group.** Oral vitamin D3 and calcium for the secondary prevention of low-trauma fractures in elderly people (randomized evaluation of calcium or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365:1621–28.
11. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL.** Vitamin D and Vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2005;(3)CD000227.
12. **Buster JE, Kingsberg SA, Aguirre O, et al.** Testosterone patch for low sexual desire in surgically menopausal women: A randomized trial. *Obstet Gynecol*. 2005;105:944–52.

Acknowledgement: The authors are grateful to Jennifer L. Hardman, BS, PharmD, for helpful advice about article selection and interpretation.

Potential Financial Conflicts of Interest: None disclosed.

REFERENCES

1. **U.S. Food and Drug Administration.** A public health advisory: Ortho Evra 2005. Available at: <http://www.fda.gov/cder/drug/infopage/orthoevra/default.htm>.
2. **Jick SS, Kaye JA, Russmann S, Jick H.** Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35mcg of ethinyl estradiol. *Contraception*. 2006;73(March): 223–8.
3. **GlaxoSmithKline Clinical Trial Register.** Available at: <http://ctr.gsk.co.uk/medicinelist.asp>. and www.gsk.com/media/paroxetine/mi_letter_paroxetine_pregnancy.pdf.
4. **Cohen LS, Altshuler LL, Harlow BL, et al.** Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006;295(5):499–507.
5. **Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al.** Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579–87.

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APPENDIX

Table 3 summarizes important women's health articles published between April 2005 and February 2006 not described in the text. Table 4 summarizes reports on women's health medications.

Table 3. Summary of women's health articles (not described in text)

Reference	Aim: clinical question	Methods	Results	Limitations	Conclusions and comments
<i>Office gynecology: contraception, pelvic exam, HPV vaccine, vaginitis, dysuria</i>					
[1]	Does St. John's wort interact with OCs?	16 women given OC (loestrin, 20 mcg ethinyl estradiol) and placebo for 2 cycles and then OC with St. John's wort 300 mg tid.	OC with St. John's wort had lower hormone levels, increased breakthrough bleeding, and increased ovarian follicle growth compared to OC with placebo.	Small, single-blinded.	St. John's wort may reduce OC effectiveness.
[2]	Does gel lubrication during vaginal speculum examination affect Pap or sexually transmitted infection test results?	Women randomized to gel-lubricated or water-moistened speculum exams: more than 3,000 conventional Pap smears and more than 5,000 DNA probes for chlamydia and gonorrhea collected.	Unsatisfactory Pap tests were similar in both groups (1.5% for water and 1.1% for gel exams). Chlamydia was detected equally (1.5%) in both groups. Gonorrhea rates were too low to analyze.	Unclear if generalizable to lubricants other than Surgilube.	Lubrication does not interfere with conventional Pap tests or detection of chlamydia. Use of lubricant may improve comfort.
[3]	Does gel lubrication during vaginal speculum examination affect liquid-based Pap results?	2 liquid-based Pap tests from each of 200 women were randomized to contamination (Surgilube gel applied to spatula and brush after specimen collection) and control.	The rate of abnormal cytology was similar between the groups (6.5% contamination vs 7% control). Number of unsatisfactory specimens similar. Similar ability to diagnose bacterial vaginosis or yeast.	A larger sample was needed to show statistical equivalence. Unclear if generalizable to lubricants other than Surgilube.	Lubrication likely does not interfere with liquid-based Pap tests.
[4]	Is a monovalent HPV-16 vaccine effective?	More than 2,000 women aged 16–23 randomized to 3 doses of HPV-16 vaccine or placebo. Followed for 4 y.	Persistent HPV-16 cases were more common in controls: 111 versus 7 in intervention group. CIN 2–3 more common in controls: 12 versus 0.	Long-term effectiveness unknown.	Efficacy of a monovalent HPV-16 vaccine is 94% for infection and 100% for CIN 2–3. Gardasil, a quadrivalent HPV vaccine (against 6, 11, 16, and 18) is now available and recommended for women aged 9–26.
[5]	Does single-dose fluconazole interact with warfarin?	6 women with stable warfarin doses were monitored after 150 mg of fluconazole.	PT increased and peaked 5 d after fluconazole (mean increase of 30%). 3 of 6 women had a clinically relevant increase in INR.	Small observational study.	Single-dose fluconazole may increase INR in women on chronic warfarin.
[6]	Do empiric antibiotics relieve dysuria in women with a normal urine dipstick?	59 women (ages 16–50) with dysuria but a negative urine dipstick test randomized to trimethoprim 300 mg daily for 3 d or placebo.	Trimethoprim relieved dysuria: 24% versus 74% controls had persistent symptoms after 3 d ($P=.005$). Median time for symptom relief was 3 d for interventions and 5 d for controls ($P=.002$).	Causes of dysuria (such as urine cultures and chlamydia testing) were not evaluated.	3 d of trimethoprim relieved dysuria in women with a normal urine dipstick. Empiric antibiotics in women with dysuria may be appropriate.
<i>Medical aspects of pregnancy: antidepressants</i>					
[7]	Is persistent pulmonary hypertension of the newborn (PPHN) associated with SSRIs?	377 infants with PPHN were matched to 836 controls. Blinded nurses conducted interviews.	14 infants with PPHN compared with 6 controls had been exposed to a SSRI (adjusted OR 6.1, 95% CI 2.2–16.8). SSRI use before 20 wk gestation and other antidepressants were not associated with PPHN.	Small number of cases. Finding needs confirmation.	PPHN occurs in about 1 out of 100 infants exposed to SSRIs late in pregnancy.
[8]	Is the neonatal behavioral syndrome associated with SSRIs?	Literature review of studies with SSRI use in the third trimester or earlier that assessed neonatal outcomes. 13 case reports and 9 cohorts identified.	Late exposure to SSRIs increased risk of neonatal behavioral syndrome: OR 3.0, 95% CI 2.0–4.4. Most cases included fluoxetine or paroxetine. Syndrome was mild.	Neonatal behavioral syndrome has multiple definitions. Cause-effect cannot be established with case reports and cross-sectional cohorts.	Third-trimester SSRI use is associated with a neonatal behavioral syndrome similar to colic.
[9]	What is the natural history of depression during pregnancy?	More than 200 pregnant women with history of major depression and current or recent use of an antidepressant but euthymic in past 3 mo. Followed monthly from their first trimester.	About 40% relapsed. Relapse was more frequent in women discontinuing antidepressants (68%) than in women continuing them (26%), $P<.001$. Younger women and women with recurrent depression were more likely to relapse.	Nonrandomized design (randomization of drug during pregnancy unethical). Cannot clearly determine temporal sequence between relapse and antidepressant discontinuation.	Depression relapse is common in pregnant women, particularly those who discontinue antidepressants.

Table 3. (continued)

Reference	Aim: clinical question	Methods	Results	Limitations	Conclusions and comments
<i>Low-fat diet and omega-3 supplements: risk of cancer and heart disease</i>					
[10]	Does a low-fat diet decrease risk of CRC?	WHI low-fat diet RCT (see text). Patient report of colon cancer confirmed, but patient report of polyps not adjudicated.	After about 8 y, 1.03% of intervention subjects developed CRC, compared to 0.95% of the control group. HR 1.08 (95% CI 0.90–1.29). The intervention group had a statistically significant 9% lower risk of developing a polyp. Intervention subjects had a 3.6-point greater decline in LDL values, a 0.4-point decline in HDL levels, and a 2.2 kg decline in weight. After 8 y, 2.9% of the intervention subjects had developed major CHD, compared to 2.9% of the control group. HR 0.98 (0.88–1.09).	Participants could also enroll in other WHI trials. 8 y may not be long enough to detect colon cancer differences in a screened population. Diet changes were modest. Secondary outcome. Saturated fats were not targeted. The small change in cholesterol levels would predict a decrease in CHD risk by only 2–4%, less than what the study was powered to detect.	A low-fat diet had no effect on colon cancer incidence over 8 y.
[11]	Does a low-fat diet decrease risk of CHD?	WHI low-fat diet RCT (see text). Major CHD defined as acute MI, silent MI or CHD death.	Intervention subjects had a 3.6-point greater decline in LDL values, a 0.4-point decline in HDL levels, and a 2.2 kg decline in weight. After 8 y, 2.9% of the intervention subjects had developed major CHD, compared to 2.9% of the control group. HR 0.98 (0.88–1.09).	Secondary outcome. Saturated fats were not targeted. The small change in cholesterol levels would predict a decrease in CHD risk by only 2–4%, less than what the study was powered to detect.	A general low-fat diet intervention had no effect on CHD in an underpowered trial.
[12]	Do diets that promote lower fat and higher carbohydrate intake promote weight gain?	WHI low-fat diet RCT (see text). Included postmenopausal women aged 50–79 y. Excluded those consuming less than 32% of energy from fat at baseline, based on self-report.	Compared to the control group, the intervention group consumed 11% less fat calories at year 1, and 8% less at year 6. The intervention group ate 1/2 serving more of grains per day. Intervention subjects lost 2.2 kg by year 1, and had 0.4 kg lower weight by 7.5 y. Results similar by age, race, and BMI.	Secondary analysis. Generalizability limited by inclusions and exclusions. Fat calories may have been overestimated by 2–3%.	A low-fat dietary intervention did not promote obesity, either overall or in subgroups. Rather, weight loss correlated with fat reduction.
[13]	Do omega-3s reduce cancer risk?	Meta-analysis of 38 articles among 20 prospective cohorts in 7 countries. 11 different cancers examined. More than 700,000 men and women.	Of 65 estimates reported, only 8 associations were statistically significant. Significant associations showed both increased and decreased incidence.	Omega-3 consumption measured 6 different ways. Gender-specific analysis not performed.	There is no association between omega-3 fatty acid consumption and cancer incidence.
<i>Breast cancer treatment</i>					
[14]	What is the best adjuvant therapy in postmenopausal, hormone-receptor-positive breast cancer: an aromatase inhibitor or tamoxifen?	Multicenter RCT of more than 8,000 comparing 4 groups: letrozole alone for 5 y, letrozole for 2 y followed by tamoxifen for 3, tamoxifen alone for 5 y, and tamoxifen for 2 y followed by letrozole for 3. This report includes the first 2 y of data, essentially comparing initial tamoxifen to initial letrozole.	Women in the letrozole groups had an estimated 5-y disease-free survival of 84% compared to 81% in the tamoxifen groups, HR 0.81 (95% CI 0.70–0.93). Women treated with tamoxifen had more thrombo-embolism, endometrial cancer, and vaginal bleeding. Women treated with letrozole had more fractures, arthralgias, and serious cardiac events (2.1% vs 1.1%).	Study is short-term. Differences in overall survival have not yet been confirmed. Adverse effect profiles are not yet fully defined for the aromatase inhibitor class of agents.	Aromatase inhibitors offer an absolute 1% per year improvement in short-term disease-free survival for postmenopausal women with hormone-receptor-positive breast cancer compared to tamoxifen. Adverse effects differ.
<i>Osteoporosis prevention: calcium and vitamin D</i>					
[15]	Does calcium and vitamin D supplementation prevent fractures in older community-dwelling women?	Unblinded RCT with 25 mo follow-up. More than 3,000 community-dwelling women over age 70 and at least one other osteoporosis risk factor. Intervention: 1,000 mg of calcium, 800 IU of vitamin D ₃ , and advice from a nurse on how to reduce risk of fracture. Control: leaflet with general advice. Self-report of fractures confirmed.	No reduction in any fractures (OR 1.01, 95% CI 0.71–1.43), hip fractures (OR 0.75, 95% CI 0.31–1.78) or hip and wrist fractures (OR 0.89, 95% CI 0.59–1.44) with supplementation.	About 60% adherence at 18 mo. Baseline calcium intake > 1,000 mg. Short-term. Underpowered. Unblinded.	In older women, there was no difference in the rate of fractures when supplementing calcium and vitamin D on top of high baseline calcium. Confirms WHI report (see text), but study limitations make conclusion uncertain.

[16]	Does calcium and/or vitamin D supplementation prevent osteoporotic fractures?	Systematic meta-analysis (Cochrane) of RCTs: 38 trials included. Men and women.	Vitamin D alone versus placebo or no treatment: no effect ($n > 18,000$). Vitamin D plus calcium versus calcium alone: no effect ($n > 6,000$). Vitamin D versus calcium: calcium better for vertebral fracture ($n = 3,000$). Vitamin D plus calcium versus placebo or no treatment: intervention better for hip fractures only. RR 0.81, 95% CI, 0.68–0.96 ($n > 10,000$). About 10% had new low-trauma fractures. No difference in the incidence of fractures among any of the groups. Compliance with calcium 10% lower than placebo because of GI symptoms.	Mx of interventions: all doses of calcium and vitamin D combined. Men and women combined. Varied quality, some unblinded, some with differences between control and intervention groups, some without dropout information. Does not include recent trials (such as WHI). No gender-specific analysis.	In this large meta-analysis, calcium plus vitamin D prevents hip fracture. In subgroup analysis, older, more frail people have the most benefit. (See text for further discussion about calcium and vitamin D).
[17]	Does vitamin D and/or calcium supplementation prevent fracture in those with a history of low-trauma fracture?	RCT of more than 5,000 community-dwelling patients (85% women) over age 70 with history of fracture. Those on bisphosphonates and calcium or vitamin D supplementation were excluded. Randomized into 1 of 4 groups: vitamin D3 800 IU + calcium carbonate 1,000 mg daily, vitamin D3 alone, calcium alone, or placebo. Followed for 24–64 mo. Fracture outcome determined by confirmed self-report and hospitalization and death records.	There was no difference in fracture risk with vitamin D, calcium, or the combination compared to placebo, in community-dwelling patients with previous low trauma fractures. In practice, these patients should be treated with antiresorptive therapy and calcium + vitamin D. (See text for further discussion about calcium + vitamin D).	Low compliance (54% at 24 mo). Respondents differed from nonrespondents. No gender-specific analysis.	The increase in BMD seen after 1 y of PTH (1–84) is lost after discontinuation of therapy if not followed by alendronate.
<i>Osteoporosis treatment: PTH</i>					
[18]	PTH stimulates bone formation during 6–12 mo of use but later increases bone remodeling. Is BMD best maintained if 12 mo of PTH (1–84) is followed by a bisphosphonate?	RCT of more than 200 osteoporotic women in 4 groups: (1) PTH for 1 y then alendronate 10 mg for 1 y, (2) PTH for 1 y then placebo for 1 y, (3) PTH and alendronate (combination group) for 1 y then alendronate for 1 y, and (4) alendronate for 2 y (control group). RCT of 126 women with osteoporosis or osteopenia and high risk of fracture, mean age 68. Randomized to 1 of 3 groups for 15 mo: (1) alendronate 70 mg weekly, (2) daily PTH (1–34) 25 mcg SQ plus alendronate, and (3) cyclic PTH (3 mo on, 3 mo off) plus alendronate.	All 4 groups had increased spine BMD; the greatest increase was with PTH then alendronate (12%) and the smallest with PTH then placebo (4%). The combination group was similar to the PTH then alendronate group. All 4 groups had increased hip BMD, excepting PTH then placebo.	Not designed to test differences in fracture rates. Study conducted in bisphosphonate-naïve women (never taken or none for > 1 y). PTH (1–84) is not available in the United States.	The increase in BMD seen after 1 y of PTH (1–84) is lost after discontinuation of therapy if not followed by alendronate.
[19]	Does PTH improve BMD and/or biochemical markers of bone turnover in women who had used or were currently taking alendronate?	RCT of 126 women with osteoporosis or osteopenia and high risk of fracture, mean age 68. Randomized to 1 of 3 groups for 15 mo: (1) alendronate 70 mg weekly, (2) daily PTH (1–34) 25 mcg SQ plus alendronate, and (3) cyclic PTH (3 mo on, 3 mo off) plus alendronate.	Spine BMD increased more in the PTH groups than the alendronate-alone group (6% vs no change, $P < .001$). Hip BMD increases did not differ between the groups. Bone formation indexes rose in both PTH groups, and most consistently in the daily PTH group.	Small study. Not designed to assess fracture rate.	In contrast to previous studies, PTH (1–34) increases BMD in women who are persistently osteoporotic after taking bisphosphonates.
<i>Osteopenia treatment</i>					
[20]	Are bisphosphonates effective in preventing vertebral fractures in osteopenic (not osteoporotic) women?	RCT of more than 2,800 osteopenic women: alendronate 5 mg/d for 2 y then 10 mg/d for about 2 y versus placebo. Mean t -score at baseline was -2.1 .	Intervention women without a previous vertebral fracture trended toward decreased risk of fracture, RR 0.46, 95% CI 0.16–1.17; 10 versus 22 cases per 10,000 person-years.	Subgroup secondary analysis of published RCT. Industry-sponsored.	Osteopenic women without history of fracture may modestly benefit from prophylactic alendronate.

Table 3. (continued)

Reference	Aim: clinical question	Methods	Results	Limitations	Conclusions and comments
[21]	Is it cost-effective to treat osteoporotic women with bisphosphonates?	Cost-effectiveness model of health effects due to fractures in osteoporotic women aged 55–75.	The lifetime incremental cost ratios (cost of gaining 1 QALY) ranged from \$70,000 to \$332,000, depending on age and <i>t</i> -scores.	Model based on best estimates of fracture rate reduction and current cost of alendronate (many assumptions). Applicable only to white women in the United States.	Assuming that the societal willingness to pay is \$50,000 per QALY, it is not cost-effective to treat osteoporotic women without previous fractures.
<i>Subclinical hypo- and hyperthyroidism: risk of heart disease</i>					
[22]	Subclinical hypothyroidism is common in women older than age 70 (about 10%). Is subclinical hypothyroidism associated with CVD in older adults?	Longitudinal cohort of more than 2,700 participants (51% women) aged 70–79 followed for 4 y. CVD diagnoses (CHF, CHD, stroke, and PAD) were adjudicated after self-report or death. 12% had subclinical hypothyroidism (TSH > 4.5 mIU/L and normal T4).	Participants with TSH > 7 were more likely to have CHF than euthyroid participants (35 vs 16 per 1,000 person-years; <i>P</i> = .006), and the strength of the association increased with higher TSH elevations. Excluding those with baseline CHF, RR of developing CHF: 2.49 (95% CI 1.20–5.18; <i>P</i> = .02). TSH was not associated with CHD, stroke, or PAD. Subclinical hypothyroidism was associated with CHD at baseline and CHD incidence: adjusted OR 1.7, 95% CI 1.2–2.4, <i>P</i> < .01. No significant outcomes associated with subclinical hypothyroidism (<i>n</i> = 39 only).	Secondary analysis. Unclear whether treatment of TSH elevations would reduce risk of CHF. Association not tested in younger ages. CHF diagnosis given only if hospitalized. Thyroid symptoms not assessed. No gender-specific analysis.	Subclinical hypothyroidism increased risk of CHF in older adults, but not other cardiovascular outcomes. How this finding, if confirmed (see below), affects screening and treatment recommendations is unclear. It is reasonable to screen both women over age 70 every 5 y and women with any thyroid symptoms. Subclinical hypothyroidism appears to increase risk of CHD 10 or more years later. This is the first study with this finding. Subclinical hypothyroidism not associated with CVD.
[23]	Is subclinical hypothyroidism or hyperthyroidism associated with CVD in adults of all ages?	Longitudinal cohort of more than 2,100 participants (50% women), age range 17–89, average 50. Followed for 20 y. 6% had subclinical hypothyroidism (TSH > 4 mIU/L and normal T4). Outcome included "CVD" (undefined) and CHD.	Subclinical hyperthyroidism (even if later treated) increased the risk of developing atrial fibrillation compared to euthyroidism (67 vs 31 events per 1,000 person-years, adjusted HR 2.0, <i>P</i> < .001). Subclinical hypothyroidism was not associated with any CVD.	CVD outcome based on diagnosis coding at clinical visits, hospitalization, or death. Effect of treatment of subclinical thyroid disorders not evaluated. Thyroid symptoms not assessed. No gender-specific analysis.	Subclinical hyperthyroidism increases risk of atrial fibrillation in older adults. Subclinical hypothyroidism is not associated with CVD risk. It is reasonable to treat subclinical hyperthyroidism (TSH < 0.1) to prevent atrial fibrillation.
[24]	Is subclinical hypothyroidism or hyperthyroidism associated with CVD in older adults?	Longitudinal cohort of more than 3,200 participants (60% women) over age 65. Followed for 13 y. 1.5% had subclinical hypothyroidism (TSH 0.11–0.44 mIU/L or TSH < 0.10 mIU/L with a normal T4); 15% had subclinical hypothyroidism (TSH 4.5–20 mIU/L). Outcomes (atrial fibrillation, CHD, or stroke) confirmed after self-report.	Symptoms were common; more so in the group formerly taking E + P compared to group formerly taking placebo (63% vs 40% had any symptom, <i>P</i> < .01). Vasomotor symptoms more common after E + P (21% vs 5%, <i>P</i> < .01), and more likely in women with previous symptoms. Musculoskeletal symptoms more common after E + P (37% vs 22%, <i>P</i> < .01). Self-selected management strategies (e.g., nonpharmacological, dietary, and clinical therapies) helpful.	Cross-sectional survey. Occurred about 1 y after trial discontinuation. Respondents differed from nonrespondents. Excluded both women unable to tolerate HT withdrawal and women electing to stop study medication (more than 40%). Time course of symptoms and whether symptomatic women had relief with E + P not explored.	Older women discontinuing E + P commonly have vasomotor, musculoskeletal, and other symptoms. It is unclear to what degree previous E + P use plays. Encouraging women to try any therapy that resonates is helpful.
<i>Postmenopausal hormones and symptoms</i>					
[25]	What are the symptoms with menopausal HT withdrawal?	Survey of more than 8,000 women aged 50–79 completing the WHI E + P trial. Included only women who had still been taking the study medication at trial completion. Primary end point was moderate-severe symptoms; checklist included 23 symptoms.			

[26]	<p>What are the benefits and adverse effects of menopausal hormones (HT)?</p>	<p>4 analyses of WHI RCT including healthy women aged 50-79: (1) cross-sectional, (2) longitudinal analysis of symptomatic women, (3) longitudinal analysis of asymptomatic women, and (4) longitudinal analysis of all women exploring vaginal bleeding.</p>	<p>Menopausal and joint symptoms increased with age. 1 y of E + P significantly relieved hot flashes (OR 4.4), vaginal dryness (OR 2.4), and joint pain and stiffness (OR 1.4). In women aged 50-54, 83% assigned to E + P and 52% assigned to placebo had vasomotor symptom relief at 1 y. 1 y of E + P significantly increased the risk of breast tenderness (OR 4.3), vaginal irritation (OR 1.5), and gynecologic surgery (0.5% vs 0.4% annualized). 51% of women had vaginal bleeding after 6 mo of E + P; spotting persisted in 10% even after 7 y.</p>	<p>Secondary analyses. Women with bothersome menopausal symptoms off estrogen excluded from the trial.</p> <p>E + P relieves hot flashes, vaginal dryness and joint pains but causes breast tenderness, vaginal irritation, and vaginal bleeding. Half of perimenopausal symptomatic women are free of symptoms after 1 y of nonspecific therapy.</p>
<i>Nonhormonal alternatives for menopausal symptoms</i>				
[27]	<p>Does gabapentin relieve vasomotor symptoms in breast cancer survivors?</p>	<p>RCT including more than 400 breast cancer survivors (average age 55) with vasomotor symptoms (average of 8 hot flashes/d). Randomized to 8 wk of placebo, 100 mg gabapentin tid, or 300 mg gabapentin tid, after a 3-d dose titration period.</p>	<p>900 mg/d of gabapentin significantly relieved hot flash frequency (2 less flashes/d) and severity (30% improvement) compared to placebo. Placebo also resulted in mild improvement (2 less flashes/d and 15% improvement in severity) compared to baseline. Dose-response trend. Few adverse effects.</p>	<p>About 70% taking tamoxifen. Unclear if generalizable to healthy women.</p> <p>300 mg of gabapentin tid relieved hot flashes in breast cancer survivors; a higher dose may be even more effective. Gabapentin may be preferable to SSRIs in women taking tamoxifen, as paroxetine reduced the circulating levels of a tamoxifen metabolite in 1 report (28).</p>
[29]	<p>Does paroxetine relieve vasomotor symptoms?</p>	<p>Multicenter crossover trial. Included more than 150 women (median age 50) with troublesome hot flashes. 80% breast cancer survivors. Randomized to 4 wk of either 10 or 20 mg of paroxetine crossed over with 4 wk of placebo. RCT of more than 300 postmenopausal women (average age 54) with symptoms. Randomized to 12 wk of black cohosh (Remifemin® twice daily) or placebo.</p>	<p>Both doses of paroxetine significantly relieved hot flash frequency (about 1.5 less flashes/d) and severity (about 25% improvement) compared to placebo. Improved sleep but not depressive symptoms or quality of life. Less nausea with 10 mg dose.</p> <p>Black cohosh significantly reduced scores on the hot flash, psyche, and atrophy subscales of the Menopause Rating Scale compared to placebo. Larger effect seen for women closer to their last menstrual period and with lower FSH. Few adverse effects.</p>	<p>10 mg of paroxetine modestly improves vasomotor symptoms.</p> <p>Black cohosh plus St. John's wort improves vasomotor symptoms and depression in depressed women with menopausal symptoms.</p>
[30]	<p>Does black cohosh relieve vasomotor symptoms after menopause?</p>	<p>RCT of more than 300 postmenopausal women (average age 54) with symptoms. Randomized to 12 wk of black cohosh (Remifemin® twice daily) or placebo.</p>	<p>Industry-sponsored. The effect size is reported in "Menopause Rating Scale units"; the clinical importance of this effect size is unknown. Analysis was "per protocol," not intention to treat.</p>	<p>Black cohosh may modestly improve menopausal symptoms in postmenopausal women.</p>
[31]	<p>Does black cohosh plus St. John's wort relieve vasomotor symptoms in depressed women?</p>	<p>RCT of more than 300 women (average age 52) with menopausal complaints and significant depression symptoms, excluding those on antidepressants or estrogenic medications. Randomized to 8 wk of twice daily black cohosh (approximately 30 mg) plus St. John's wort (approximately 300 mg) or placebo, followed by 8 wk of the same tablets once daily.</p>	<p>16 wk of trial cannot evaluate long-term safety of black cohosh or St. John's wort.</p>	<p>Black cohosh plus St. John's wort improves vasomotor symptoms and depression in depressed women with menopausal symptoms.</p>

Table 3. (continued)

Reference	Aim: clinical question	Methods	Results	Limitations	Conclusions and comments
<i>Heart disease: postmenopausal hormones, primary prevention</i>					
[32]	Is CVD risk the same with esterified and CEE?	Case-control study based on a couple formulary changes in a large HMO. Cases were about 1,600 postmenopausal women with incident MI and about 1,000 women with incident CVA (found by hospitalization diagnosis or cause of death). Controls (about 3,500) were matched for age and treated hypertension. Average age 67–70.	In analyses excluding nonusers, CEE did not have significantly different risks than esterified estrogens for MI or CVA. In secondary analyses, esterified estrogens tended to fare better than CEE when without progesterin, at estrogen doses higher than 0.625 mg, and within 3 mo of prescription.	Multiple comparisons. Case-control study.	Esterified estrogens have marginal benefit in secondary analyses of CVD risk compared to CEE. Neither estrogen (with or without progesterin) conferred any risk of MI or CVA in this observational study.
[33]	Is there a gender difference in the effect of aspirin for primary prevention?	Meta-analysis of 6 RCTs and more than 90,000 participants using aspirin without CVD (defined as MI or CVA). 3 trials included only men, 1 trial included only women, and 2 included both sexes.	Both women and men reduced their risk of CVD: women, OR 0.88, 95% CI 0.8–1.0, $P=.03$; men, OR 0.86, 95% CI 0.8–0.9, $P=.01$. Aspirin reduced the risk of MI for men (OR 0.68, $P=.001$) but not women (OR 1.01, $P=.95$). Aspirin reduced the risk of ischemic CVA for women (OR 0.76, $P=.008$) but not men (OR 1.00, $P=.98$). Aspirin did not affect hemorrhagic stroke in women but increased this risk in men. Aspirin increased the risk of major bleeding events similarly in both genders (OR 1.7).	Variety of aspirin doses. Only 3 trials including women (5 including men).	Aspirin prevents ischemic strokes in women and MIs in men, while increasing bleeding events in both. Benefits over risks are modest for primary prevention in a low-risk population: 6 y of aspirin therapy prevents 3 CVD events per 1,000 women and 4 CVD events per 1,000 men, but causes about 2.5 major bleeding events in women and 3 in men.
<i>Sexual function</i>					
[34]	Does testosterone increase libido in oophorectomized women on estrogen?	RCT of 300 mcg/d testosterone patch versus placebo for 6 mo in more than 550 women without ovaries and on estrogen. (Methods parallel trial in text).	With testosterone, women had about 0.2 more satisfying sexual encounters weekly and about a 10-point (out of 100) increase in sexual desire score compared to placebo. Androgenic adverse events (acne, facial hair, alopecia, and voice deepening) were higher in the testosterone group, 20% versus 11% (P value not given).	Industry sponsored. Testosterone patch product not commercially available.	Testosterone patch appears to modestly increase libido in surgically menopausal women. Androgen adverse events were common.
[35]	Do low levels of circulating androgens predict sexual dysfunction?	Healthy, nonpregnant Australian women were recruited from a defined population to maintain an equal distribution of ages between 18 and 75. Low sexual functioning was defined as 0 on a 100-point sexual functioning scale in any of 7 domains (arousal, pleasure, orgasm, desire, responsiveness, self-image, and sexual concerns).	About 5% of women in the younger age group (18–44 y) had low sexual functioning compared to 4–18% of women in the older age group (45–75 y). The domains of arousal, pleasure, and orgasm were more likely to have low scores. Total and free testosterone levels did not predict low sexual functioning. DHEAS levels correlated in some domains, but the majority of women with low DHEAS did not report sexual dysfunction.	This study did not address how hormone levels could be used to guide therapy in women with low sexual function.	Measurement of testosterone or DHEAS levels is not clinically informative in predicting low sexual function.

BMD = bone mineral density, CEE = conjugated equine estrogens, CHD = coronary heart disease, CHF = congestive heart failure, CI = confidence interval, CIN = cervical intraepithelial neoplasia, CRC = colorectal cancer, CVD = cardiovascular disease, DHEAS = dehydroepiandrosterone sulfate, E + P = estrogen + progesterin, HR = hazard ratio, HT = hormone therapy, INR = International Normalized Ratio, OC = oral contraceptives, OR = odds ratio, PAD = peripheral artery disease, PTH = parathyroid hormone, QALY = quality-adjusted life year, RCT = randomized controlled trial, RR = relative risk, SRI = serotonin-reuptake inhibitor, SSRI = selective serotonin-reuptake inhibitors, WHI = Women's Health Initiative

Table 4. Brief reports on women's health medications: new information on administration and adverse effect profile for unique preparations

Product (generic, brand name)	Finding (reference)	Comment
Contraceptive patch, OrthoEvra	12-wk extended use of patch decreases menstrual bleeding [36]	Nonsignificant increases in headache, nausea, and breast tenderness with extended use.
Contraceptive ring, NuvaRing	6-wk extended use of the contraceptive ring decreases menstrual bleeding [37]	12- and 51-wk extended use also decreased menstrual bleeding, but bothersome spotting led to a high rate of discontinuation.
DMPA, DepoProvera	Self-administration acceptable to women in Scotland [38]	A DMPA subcutaneous dose (104 mg rather than 150 mg IM) was approved by the FDA in 2005.
DMPA, DepoProvera	Same-day administrative protocol increases use [39]	Protocol: women offered choice to return for injection within first 5 d of next menses to be sure of non-pregnant state; emergency contraception given if unprotected intercourse within 5 d; pregnancy test; if negative, DMPA given with backup contraception for d; pregnancy test repeated at next visit.
Estradiol/drospirenone 1/3 mg, Angeliq	Lowered blood pressure in hypertensive postmenopausal women by 14/8 [40]	Drospirenone is a novel progestin with antimineralocorticoid and antiandrogen activity; it is the progestin in the oral contraceptive Yasmin.
Ultralow-dose estrogen patch 0.014 mg/d estradiol, Menostar	Does not cause incontinence unlike other estrogens [41]	Ultra low-dose approved only for osteoporosis prevention; it does not treat menopausal symptoms.

DMPA = depomedroxyprogesterone acetate

Appendix References

- Murphy PA, Kern SE, Stanczyk FZ, et al. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception*. 2005;71:402-8.
- Griffith WF, Stuart GS, Gluck KL, et al. Vaginal speculum lubrication and its effects on cervical cytology and microbiology. *Contraception*. 2005;72(1):60-4.
- Hathaway JK, Pathak PK, Maney R. Is liquid-based Pap testing affected by water-based lubricant? *Obstet Gynecol*. 2006;107(1):66-70.
- Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia. *Obstet Gynecol*. 2006;107(1):18-27.
- Turrentine MA. Single-dose fluconazole for vulvovaginal candidiasis: Impact on prothrombin time in women taking warfarin. *Obstet Gynecol*. 2006;107(2):310-3.
- Richards D, Toop L, Chambers S, et al. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double-blind randomized controlled trial. *Br Med J*. 2005;331:143-6.

7. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579-87.

8. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA*. 2005;293(19):2372-83.

9. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006;295(5):499-507.

10. Beresford SA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, et al. Low-fat dietary pattern and risk of colorectal cancer. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:643-54.

11. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and risk of cardiovascular disease. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655-66.

12. Howard BV, Manson JE, Stefanick ML, Beresford SA, Frank G, et al. Low-fat dietary pattern and weight change over 7 years. The Women's Health Initiative Modification Trial. *JAMA*. 2006;295:39-49.

13. MacLean CH, Newberry SJ, Mojica WA, et al. Effects of omega-3 fatty acids on cancer risk. A systematic review. *JAMA*. 2006;295:403-15.

14. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353:2747-57.

15. Porthouse J, Cockayne S, King C, et al. Randomized controlled trial of calcium and supplementation with cholecalciferol (Vitamin D3) for the prevention of fractures in primary care. *Brit Med J*. 2005;300:1003-8.

16. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2005;(3):CD000227.

17. The Record Trial Group. Oral vitamin D3 and calcium for the secondary prevention of low-trauma fractures in elderly people (randomized evaluation of calcium or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet*. 2005;365:1621-28.

18. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med*. 2005;353(6):555-64.

19. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med*. 2005;353(6): 566-75.

20. Quandt SA, Thompson DE, Schneider SL, Nevitt MC, Black DM. Effect of alendronate on vertebral fracture risk in women with bone mineral density t score of -1.6 to -2.5 at the femoral neck: The Fracture Intervention Trial. *Mayo Clin Proc*. 2005;80:343-9.

21. Schousboe JT, Nyman JA, Kane RL, Ensrud LKE. Cost effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med*. 2005;142(9):734-42.

22. Rondoni N, Newman AB, Vittinghof E, et al. Subclinical hypothyroidism and the risk of heart failure. Other cardiovascular events and death. *Arch Intern Med*. 2005;165:2460-6.

23. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med*. 2005;165:2467-72.

24. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295(9):1033-41.

25. Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA*. 2005;294:183-93.

26. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol*. 2005;105:1063-73.

27. Pandya KJ, Morrow GR, Roscoe JA, Zhao H, Hickok JT, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. *Lancet*. 2005;366:818-24.

28. Stearns V, Johnson MD, Rae JM, Moroch A, Bhargava AP, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003;95:1758-64.

29. **Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, et al.** Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol.* 2005;23:6919-30.
30. **Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, et al.** Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol.* 2005;105:1074-83.
31. **Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruewald J, Wernecke KD.** Black cohosh and St. John's wort for climacteric complaints: a randomized trial. *Obstet Gynecol.* 2006;107:247-55.
32. **Lemaitre RN, Weiss NS, Smith NL, et al.** Esterified estrogen and conjugated equine estrogen and the risk of incident myocardial infarction and stroke. *Arch Intern Med.* 2006;166:399-404.
33. **Berger JS, Roncaglioni M, Avanzini F, Pangrazzi I, Tognoni G, Brown DL.** Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA.* 2006;295:306-13.
34. **Buster JE, Kingsberg SA, Aguirre O, et al.** Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol.* 2005;105:944-52.
35. **Davis SR, Davidson SL, Donath S, Bell RJ.** Circulating androgen levels and self-reported sexual function in women. *JAMA.* 2005;294: 91-6.
36. **Stewart FH, Kaunitz AM, LaGuardia KD, et al.** Extended use of transdermal norelgestromin/ethinyl estradiol: a randomized trial. *Obstet Gynecol.* 2005;105(6):1389-96.
37. **Hout J, Miller L, Verhoeven CH, et al.** Extended regimens of the contraceptive vaginal ring. *Obstet Gynecol.* 2005;106(3):473-82.
38. **Lakha F, Henderson C, Glasier A.** The acceptability of self-administration of subcutaneous Depo-Provera. *Contraception.* 2005;72:14-8.
39. **Balkus J, Miller L.** Same-day administration of depot-medroxyprogesterone acetate injection: a retrospective chart review. *Contraception.* 2005;71:395-8.
40. **White WB, Pitt B, Preston RA, Hanes V.** Antihypertensive effects of drospirenone with 17 β -estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension. *Circulation.* 2005;112: 1979-84.
41. **Waetjen LE, Brown JS, Vittinghoff E, Ensrud KE, Pinkerton JA, et al.** The effect of ultralow-dose transdermal estradiol on urinary incontinence in postmenopausal women. *Obstet Gynecol.* 2005;106:946-52.