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INSIDE

The WHI and Cognition

ABSTRACTS & COMMENTARY

THE WOMEN'S HEALTH INITIATIVE REPORTED THEIR RESULTS ON cognition and dementia combining the canceled estrogen-only arm with the canceled estrogen-progestin arm of the randomized trial; the data are derived from an ancillary study of the trial entitled The Women's Health Initiative Memory Study (WHIMS). It should be emphasized that the participants in WHIMS were 65-79 years old when they entered the study. In the estrogen-only arm of WHI, 2947 women, and in the estrogen-progestin arm, 4532 women were enrolled in WHIMS (*see Table*). The participants in both arms were pooled for analysis. Half the cases were classified as Alzheimer's disease, the rest were mostly vascular dementia or mixed Alzheimer's and vascular. In the estrogen-only arm, 1464 women in the treated group were available for analysis, 1483 in the placebo group; in the estrogen-progestin arm, there were 3693 women in the treated group and 3786 in the placebo group (Shumaker SA, et al. *JAMA*. 2004;291:2947-2958; Espeland MA, et al. *JAMA*. 2004;291:2959-2968).

Table

WHIMS Results

	Estrogen-only		Estrogen-Progestin		Pooled	
	Estrogen	*Placebo*	*E-P*	*Placebo*	*Treated*	*Placebo*
Dementia	28 (cases)	19	40	21	68	40
Hazard Ratio Based on rate Per 10,000 Woman-years	1.49 (0.83-2.66)		2.05 (1.21-3.48)		1.76 (1.19-2.60)	
Probable Dementia or Mild Cognitive Impairment	93	69	85	63	178	132
Hazard Ratio Based on rate Per 10,000 Woman-years	1.38 (1.01-1.89)		1.44 (1.04-1.99)		1.41 (1.12-1.76)	

COMMENT BY LEON SPEROFF, MD

These results from the WHI do not differ substantially from the

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previous report a year ago when the WHI concluded that estrogen-progestin therapy increased the risk for probable dementia in women aged 65 years and older and did not prevent mild cognitive impairment.[1,2] However, the only statistical significant finding in that report was increased dementia in elderly women (22 cases in the treated group and 10 cases in the placebo group) who were 75 and older and who had been exposed to a relatively short-term of estrogen-progestin therapy.

In the current report, the authors responsibly point out in their discussion that this study "may not represent primary prevention of Alzheimer's disease."[3] Will older women who have used hormone therapy for long durations early in their postmenopausal years be protected against dementia? The WHI recognized that this hypothesis could not be tested in this clinical trial because of the older age of the study participants. A prospective study of a homogeneous population in Utah (thus minimizing, if not eliminating, the healthy user bias) concluded that a reduction in the risk of Alzheimer's required long-term treatment, initiated at least 10 years before symptoms of dementia appear.[4] The favorable effects of hormone therapy on cognition and the risk of Alzheimer's disease appear to be limited to women who initiate treatment close to their menopause.

Also worth noting in the current WHI report was an increase in dementia in the women with diabetes and hypertension in contrast to no increase in women without hypertension and without a history of diabetes. This emphasizes that the negative effects reported were concentrated in older women with pre-existing disease. Unfortunately, an analysis by age groups was not provided, probably because the small number of cases precluded subgroup analysis.

All cases of dementia diagnosed locally in 39 centers, and 50% of the cases of mild cognitive impairment were centrally adjudicated. Agreement in diagnoses was present in about 75% of the cases. Most disagreements resulted in a less serious classification, lowering the hazard ratio for dementia in the pooled participants to 1.54 (1.08-2.21).

In the WHIMS assessment of mental state, differences between treated and placebo groups emerged after 2 years of follow-up.[5] The overall increased risk of impaired cognition in the estrogen-only arm was estimated to be 1.47 (1.04-2.07). The adverse effect was concentrated (if not limited) in the participants who had the lowest scores on the mental state test at baseline! Also of note, an as-treated analysis of adherent participants yielded smaller differences. This is a small effect, found in older women (the mean age in WHIMS was 71), exposed to what may be a dose of estrogen relatively high for this age group. Indeed, the WHI authors even state that this difference is "too small to have relevance in clinical practice."

Whether these effects are limited to women with pre-existing cerebrovascular disease is a question that hopefully will be answered when the WHI analyzes their data from magnetic resonance imaging. In addition, long-term follow-up of the youngest postmenopausal women in the overall WHI trial may eventually provide helpful information (but at least 10 or more years from now).

Keep in mind that the participants in the 2 arms of the overall trial were not identical.[6] Specifically, the women in the estrogen-only arm had more already-diagnosed cardiovascular disease and greater previous use of hormone therapy, but at the same time, because of hysterectomies and oophorectomies, probably greater exposure to estrogen deficiency earlier in life. Therefore, the appropriateness of combining the 2 canceled arms of the trial (a maneuver designed to gain statistical power) can be questioned.

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It is appropriate to conclude that hormone therapy equivalent to an estrogen dose of 0.625 mg conjugated estrogens does not improve cognitive function in older postmenopausal women. This dose of estrogen may adversely affect cognition in women with pre-existing cerebrovascular disease. One cannot disagree, therefore, with the conclusion that this dose of estrogen should not be initiated in women over age 65 in the expectation that deterioration in cognition will be prevented. ■

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Vasa Previa: The Effect of Prenatal Diagnosis on Outcomes

ABSTRACT & COMMENTARY

Synopsis: *Good outcomes with vasa previa depend primarily on prenatal diagnosis and cesarean delivery at 35 weeks of gestation or earlier should rupture of membranes, labor, or significant bleeding occur.*

Source: Oyelese Y, et al. *Obstet Gynecol*. 2004;103: 937-942.

Oyelese and colleagues recently collected data to assess the clinical effect of diagnosing vasa previa prior to delivery. Their findings, though not surprising, were dramatic.

The group went to a repository of vasa previa information, the Vasa Previa Foundation, and to 6 large centers in order to collect data on 155 pregnancies complicated by vasa previa. The diagnosis was ultimately made in all cases by pathology. The idea was to compare outcomes in those who had the ultrasound diagnosis before delivery compared with those who did not.

The perinatal survival in the prenatally diagnosed cases was 96% (59/61) vs 44% (41/94) when not diagnosed by ultrasound. As expected, mean 1 and 5 minute Apgar scores were 1 and 4 in the undiagnosed group and 8 and 9 in the diagnosed group. Also, half of the undiagnosed surviving neonates needed transfusions.

COMMENT BY JOHN C. HOBBINS, MD

The only way to avoid mortality and morbidity in vasa previa is to deliver by Cesarean prior to rupture of membranes; so it is no surprise that virtually all perinatal disasters could have been avoided by fore knowledge of this condition.[1,2] However, now with large enough numbers, it confirms that looking for the cord insertion, especially in low-lying placentas, is worth the effort, even if the incidence of vasa previa in the overall population is said to be in 1 in 2500.

The American Institute of Ultrasound in Medicine/American College of Radiology (AIUM/ACR) guidelines for the performance of a basic ultrasound examination does not include locating the umbilical cord insertion on the placenta. However, it should, since in vasa previa the simple task can be life-saving. Also, since marginal or velamentous insertions of the cord are associated with a higher incidence of intrauterine growth retardation (IUGR), this is information that would be useful to the alert clinician.

In placenta previa, vasa previa may actually evolve as pregnancy progresses. It is well known that low-lying placentas will seemingly move away from the cervix with lengthening of the lower uterine segment. However, years ago Bernischke postulated that another phenomenon, which he labeled "trophotropism," could contribute to this relative placental migration.[3] The theory is that in some areas of the uterus, such as the lower uterine segment and cervix, the vascular environment is poorly suited to support placental development, so the placenta preferentially grows superiorly as pregnancy progresses while atrophying inferiorly. However, the umbilical cord may keep its relationship with the cervix, but lose its placental cushion, thereby finding itself in the membranes directly over the cervix.

Another condition that lends itself to vasa previa is an accessory lobe in which the connecting fetal vessels course over the cervix. This carries the same potential for disaster as an umbilical cord insertion in this area.

Although the reason for this is unclear, there is an inordinately high risk of vasa previa in (in vitro fertilization) IVF pregnancies. In one study, the rate was 1:293 IVF pregnancies vs 1:6000 in spontaneously conceived pregnancies. This is yet another example of the less than welcoming intrauterine environment inherent in some pregnancies resulting from assisted reproductive technology (ART).

It generally takes seconds to find the cord insertion site in the placenta (even without color Doppler) and I think that in every scan an attempt should be made to do this. If the cord appears to be inserting in the neighborhood of the cervix, then the diagnosis of vasa previa

could be confirmed by transvaginal ultrasound. If the diagnosis is made early in pregnancy, then it should be confirmed prior to 35 weeks of gestation since, as pointed out above, the relationship of the placenta, cord, and cervix can change in later pregnancy.

In the Oyelese study, the average gestational age at delivery for the prenatally diagnosed vasa previa was 34.9 weeks, compared with 38.2 weeks for the undiagnosed vasa previa. They make a pitch for interruption of pregnancy around 35 weeks, and from their data I agree. ■

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Prediction of Optimal vs Suboptimal Cytoreduction of Advanced-Stage Serous Ovarian Cancer with the Use of Microarrays

ABSTRACT & COMMENTARY

Synopsis: *These data support the hypothesis that favorable survival that is associated with optimal debulking of advanced ovarian cancers is due to, at least in part, the underlying biologic characteristics of these cancers.*

Source: Berchuck A, et al. *Am J Obstet Gynecol*. 2004; 190(4):910-925.

The ability to characterize the expression of thousands of genes simultaneously has provided new insight into the underlying biology of disease for many cancers. Berchuck and colleagues adapt the technology to evaluate its ability to predict primary surgical outcome in patients with newly diagnosed ovarian cancer. RNA from 44 preselected advanced (21 with survival less than 3 years and 23 with survival more than 7 years) and 5 early stage ovarian cancers were evaluated with the Affymetric Gene Chip containing 22,283 genes for their relative expression among patients achieving optimal vs suboptimal cytoreduction. The top 120 differentially expressed genes were then used to generate a prediction model, which was validated in an out-of-sample process. Specific probability models were generated for gene set in order to optimize the ability to distinguish cytoreductive outcome (19 optimal vs 25 suboptimal and 5 early stage). Berchuck and colleagues identified 32 differentially expressed genes in the optimized prediction model. Patients' cytoreductive outcome was correctly classified by the model in 72.7% of cases. Five of 25 (20%) suboptimal cases, 7 of 19 (37%) optimal cases as well as 2 of 5 (40%) stage I cases were misclassified. There was no relationship between misclassified cases and clinical or pathologic features. Evaluation of gene clusters in this set did not improve the predictive power. Berchuck et al conclude that these data do support the hypothesis that optimal cytoreduction is associated with prolonged survival and that at least in part, optimal status is due to underlying biological characteristics.

■ COMMENT BY ROBERT L. COLEMAN, MD

There are many factors which, by retrospective and prospective evaluation, have shown to be important in estimating survival in newly diagnosed or suspected ovarian cancer patients. The most recognizable, perhaps, is cytoreductive status following primary surgery; that is, the amount of residual disease following a maximal effort at removing it. In the last 30 years since the relationship was first well documented, many authors have correlated preoperative findings such as bulky radiographic disease, CA-125 levels and distribution of disease with the ability to render a patient "optimal."[1-5] While some of these factors have proven to be useful in certain circumstances (eg, patients with poor performance status) relying on them exclusively to triage patients for surgery would exclude a significant fraction (up to 30%) of debulkable patients, potentially lowering their survival by withholding an important part of their treatment package.

Most gynecologic oncologists appreciate that some tumors are just not "debulkable" and some patients rendered "optimal" have shorter than expected survivorship. Conversely, some "suboptimal" patients survive for extended periods of time—a measure of their chemosensitivity. The most frequently cited reason for these clinical observations is tumor biology—some underlying, tumor-specific feature or features that define the clinical behavior of a tumor. In the current article, Berchuck et al tackle this conundrum with state-of-the-art molecular profiling using a gene chip array. Since all human cancer appears to result from accumulating genetic mutation, studying patterns of thousands of genes simultaneously allows one to gain an insight, at

the moment of tissue harvest, of the RNA being either over or under produced relative to "maintenance" standards. The technology has already proven beneficial in producing risk classifications for patients with prostate and breast cancer. There are currently a handful of similar array studies being conducted in ovarian cancer specimens evaluating risk analysis, survival and chemosensitivity.

Berchuck et al address the biology question (via the surrogate of debulking status) by evaluating a small cohort of patients (n = 44) dichotomized by their survival (less than 3 years vs greater than 7 years) collected from a previous study by which the gene chip technology was used to investigate patterns predicting survival. The primary end point of the current trial was to evaluate the expression profile of those rendered surgically optimal against those left with greater than 1 cm of residual disease. One hundred twenty genes were differentially expressed in these 2 cohorts and made up the sample from which a prediction model was constructed. Using novel statistical and probability methodology, 32 genes were subsequently teased out, optimizing the model predicting surgical outcome. In all, the accuracy in distinguishing optimal from suboptimal was 72.7%. Although the data support proof-of-concept—that is, a genetic expression profile underlies the clinical outcome found at surgery and suggest a biological component may render tumors less debulkable, the predictive power of the model is similar to that achieved with fairly unsophisticated tools such as serum CA-125 and radiographic assessment. Unfortunately, it did not completely segregate the early stage (and therefore, optimal by nature) cases nor control for optimal as a result of stage (eg, Stage IIIA and IIIB) or surgical effort. In addition, fresh tissue cores are needed making the technique less palatable as a preoperative tool. It is also unknown whether the current model or expression profile is generalizable to the population at large given the polarized profile of the sampled cases. Nonetheless, review of individually under- or over-expressed genes reveals important clues as to what biological processes are ongoing in dysregulated growth and metastases.

It is clear we have just scratched the surface of understanding the genomic-wide events that lead up to and characterize phenotypic behavior of individual tumors. And this is just the genomic level! Since their products, (ie, proteins) drive the real cellular machinery, similar profiling will ultimately provide the level of detail needed to ferret out individual characterizations of clinical behavior. This type of proteomic analysis is now being validated in ovarian cancer screening trials. It is hoped new technologies will make detailed analysis available to patients diagnosed with ovarian cancer enabling a tailored therapeutic program, truly maximizing tumor cytotoxicity while minimizing the effects of treatment. ■

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Special Feature

Postmenopausal Hormone Therapy and the Risk of Ovarian Cancer

By Leon Speroff, MD

The canceled estrogen-progestin arm of the Women's Health Initiative reported an increase in ovarian cancer that was not statistically significant, prompting the authors to say: "The possibility of an increased risk of ovarian cancer incidence and mortality remains worrisome and needs confirmation."[1]

	Estrogen-Progestin	Placebo	Hazard Ratio
Cases	20	12	1.58 (0.77-3.24)
Deaths	9	3	2.70 (0.73-10.0)

The Kaplan-Meier curves suggested an increasing effect over time, but this, too, was not statistically significant. There were no differences reported in histologic type, stage, or grade (but the small numbers make it essentially impossible to assess subcategories). It is of importance to note that there were 2 endometrioid cancers in the treated group and none in the placebo group.

Although the lifetime risk of ovarian cancer is small, the prevalence of postmenopausal hormone therapy combined with an increase in the risk of ovarian cancer could yield an increase that would be of public health significance. For this reason, it is useful to review the recent epidemiologic data on this important issue. There have been 20 case-control studies and 4 cohort studies assessing the relationship between postmenopausal hormone therapy and the risk of ovarian cancer.[2] The relative risks encompass a wide range from below 1.0 to greater than 1.0. Two limitations are immediately apparent. The data reflect largely the use of estrogen without a progestin;

only a small number of cases exposed to estrogen-progestin are available. In addition, because this is a relatively infrequent cancer, all studies have been hampered by relatively small numbers.

The studies have found it difficult to control for all of the factors that influence the risk of ovarian cancer. This is because there are multiple factors and information regarding each factor is not readily available.

Factors That Decrease the Risk of Ovarian Cancer

- Use of steroid hormone contraceptives;
- Pregnancy and parity; a greater effect with a recent pregnancy and pregnancy at older age;[3]
- Breastfeeding;[4]
- Hysterectomy and tubal ligation;[5]
- NSAIDs.[6]

Factors That Increase the Risk of Ovarian Cancer

Increasing BMI;[7]
Infertility;[8]
Caffeine intake;[9]
Two or more eggs per week;[10]
Family history of ovarian and breast cancer;
Mixed Reports on Decreased Risk;
Alcohol intake;[11]
Mixed Reports on Increased Risk;
Cigarette smoking.[12,13]

RECENT STUDIES

Case-Control Studies

Australian Case-Control Study.[14]

Estrogen only	RR = 1.27 (0.86-1.88)
E-P	RR = 1.34 (0.83-2.17)

Summary: No significant overall effect.

Note: The only significant increase was in 18 cases with endometrioid cancer.

Italian Case-Control Study.[15]

	Cases	Controls	Relative Risk
Ever use, estrogen only	62	151	1.1 (0.8-1.5)
Use > 2 yrs	22	45	1.4 (0.8-2.5)

Summary: No significant effect.

Swedish Case-Control Study—Borderline Tumors.[16]

	Cases	Controls	Relative Risk
Estrogen only	19	259	1.63 (0.95-2.79)
Sequential E-P	19	348	1.15 (0.59-2.24)
Continuous E-P	13	280	0.59 (0.23-1.53)

Summary: No significant effect.

Swedish Case-Control Study—Invasive Tumors.[17]

	Cases	Controls	Relative Risk
Estrogen only	59	259	1.43 (1.02-2.00)
Sequential E-P	87	348	1.54 (1.15-2.05)
Continuous E-P	55	280	1.02 (0.73-1.43)

Summary: A significant small increase with estrogen-only and sequential E-P, but not with continuous E-P.

NOTE: 302 of 617 (49%) cases were endometrioid cancers.

Pittsburgh Case-Control Study.[18]

	Cases	Controls	Relative Risk
Ever use	484	926	0.94 (0.74-1.19)

Summary: No significant effect; no increase with duration; no differences with CEE compared to other estrogens; no increase with E-P.

Cohort Studies

American Cancer Society Prospective Mortality Study.[19]

	No. of Deaths	Rate Ratio
Ever use, estrogen only	255	1.51 (1.06-1.43)
< 10 yrs.	31	1.14 (0.79-1.65)
10+ yrs.	31	2.20 (1.53-3.17)

Summary: A significant increase with long duration of therapy.

Problems: No data on type of therapy; information from a single questionnaire in 1982; not controlled for risk factors; users not identical to nonusers (more use of OCs, more smokers, more tubal ligations, more educated, fewer children, thinner).

Breast Cancer Detection Demonstration Project Cohort.[20]

	Cases	Relative Risk
Estrogen only	120	1.60 (1.20-2.00)
E-P	18	1.10 (0.64-1.70)
Duration of use		
10-19 yrs.	21	1.80 (1.10-3.00)
20+ yrs.	16	3.20 (1.70-5.70)

Table continued on next page

Continued from last page

Summary: A significant increase with estrogen-only, linked to duration of use.

Problems: Adjusted only for OC use; increase with duration only in hysterectomized women; product names and doses missing for two-thirds of users; 58% of cases came from women recommended to have surgery or had surgery for breast lumps. When analyzed according to histology, only endometrioid cancer was significantly increased (7 cases; RR = 5.5, CI = 1.9-16.2).

Pooled Case-Control Studies

European Collaborative Analysis of 4 Case-Control Studies.[21]

	Cases	Controls	Odds Ratio
Ever use, estrogen only	109	146	1.71 (1.30-2.25)

Summary: A significant increase.

European Collaborative Analysis of 5 Case-Control Studies.[22]

	Cases	Controls	Odds Ratio
Ever use, estrogen only	171	287	1.28 (1.05-1.56)

Summary: A small significant increase.

Meta-Analyses

Meta-analysis of 12 case-control studies, 1992.[23]

Hospital-based:	RR = 0.90 (0.70-1.30)
Population-based:	RR = 1.10 (0.90-1.40)

Meta-Analysis of 9 Studies on Invasive Cancer Selected from 27, 1998.[24]

Ever use:	RR = 1.16 (1.03-1.29)
10+ yrs.	RR = 1.27 (1.00-1.61)

Test for trend for increasing risk with duration of use: not significant.

Meta-Analysis of 15 Case-Control Studies, 2000.[25]

Overall RR = 1.10 (0.90-1.30)

4 US studies with community controls: RR = 1.30 (1.00-1.60)

Summary: A borderline, significant increase in one meta-analysis with long duration of use; problems with all meta-analyses: assumed that controlling for risk factors was uniform in all studies.

It should also be noted that in one randomized trial and 2 retrospective cohort analyses, no detrimental effect on prognosis after surgery for ovarian cancer could be detected in patients subsequently treated with hormones.[26-28]

CONCLUSION

A major problem has been the effect of endometrioid cancers, an ovarian cancer that logically can be expected to be influenced by estrogen therapy. In many of the studies, the overall results are swayed by the increase in endometrioid cancers, a cancer that could originate in hormonally-stimulated endometriosis.[29] An accurate analysis requires a separate consideration of endometrioid cancers, but this is difficult because the small numbers do not allow effective sub-categorization.

Another concern is the time line associated with the development of ovarian cancer. The study of ovarian cancer in the atomic bomb survivors documented that the disease increased 25 years later.[30] How could postmenopausal hormone therapy produce an effect rapidly, especially because so few women have maintained therapy for many years, unless there is an effect on preexisting malignant cells?

It is not difficult to review these numbers and conclude that there is no uniform story, that there are studies with both positive and negative results, and that all of the studies struggle with limited power because of small numbers and confounding because of the difficulties in assessing and controlling for risk factors. The case-control and cohort studies irregularly controlled for level of education, parity, OC use, BMI, tubal ligation, and family history of ovarian and breast cancer (not a single study controlled for all known risk factors!). It is appropriate to emphasize the weak associations and the mixed story, but at the same time the seriousness of the specific relationship dictates that postmenopausal hormone therapy and the risk of ovarian cancer remains an unresolved issue. ■

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CME Question

4. The following statements are true regarding the WHIMS study from the WHI:

a. WHIMS enrolled only older postmenopausal women.
b. Postmenopausal women treated with hormone therapy have an increased risk of dementia.
c. WHIMS and the overall WHI study of cardiovascular disease are not primary prevention trials.
d. The risk of a deterioration in cognition was concentrated in women with cardiovascular disease and a lower level of cognition at baseline.

Answer: 4 (b)

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PHARMACOLOGY WATCH

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The Importance of Publishing Negative Clinical Studies

Sources of funding for pharmaceutical research has come under scrutiny in the last decade as academic and government sources of funding have become increasingly scarce and the pharmaceutical industry has become the main source of research dollars. But the issue of objectivity has been raised, and some have even suggested that negative studies, that is studies that show a drug in an unfavorable light, may never be published. The American Medical Association has recently tackled this issue and has asked the department of Health and Human Services to establish a public registry of all clinical trials in United States. The registry would include information regarding the design of the study and the questions to be addressed. The registry would also contain data about the study results, both positive and negative. Some members of Congress have indicated interest in pursuing legislation to create such a registry, and even large pharmaceutical companies such as Merck and GlaxoSmithKline support the concept. But despite the AMA's valid concerns, several negative studies have been newsworthy in the last 2 months. This issue of *PharmWatch* highlights a few of those.

Cognitive Effects of Estrogen Therapy

Two studies in the *Journal of the American Medical Association* suggest that estrogen alone therapy may be associated with a decline in cognitive function in post-menopausal women and may increase the risk of dementia. Both studies are follow-ups from the Women's Health Initiative Memory Study (WHIMS) which had previously shown that estrogen plus progesterone therapy increases the risk of dementia in postmenopausal women. The first study was a follow-up of nearly 3000 women randomized in a double-blind fashion to conjugated estrogen, conjugated estrogen plus progesterone, or placebo. In the estrogen alone wing, 28 women taking estrogen developed probable dementia vs 19 assigned to placebo (HR, 1.49; 95% CI, 0.83-2.66). Similar rates were noted in the estrogen plus progesterone wing. When data were pooled for both estrogen and estrogen plus progesterone, the overall hazard ratio for dementia was 1.76 (95% CI, 1.19-2.60; P = .005). Increased risk of mild cognitive impairment was also noted in the estrogen alone group and the estrogen plus progesterone group. When the data were pooled, the hazard ratio for mild cognitive impairment was 1.25 (95% CI, 0.97-1.60). This study showed that there is no difference between estrogen alone vs estrogen plus progesterone therapy in the risk of dementia or mild cognitive impairment, and in fact, both therapies increase the risk of both these end points (*JAMA*. 2004;291:2947-2958). The second study asked whether estrogen alone alters global cognitive function in postmenopausal

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women. During a mean 5.4 years of follow-up, nearly 3000 women were randomized to 0.625 mg of conjugated estrogen or matching placebo per day. The women were assessed annually with the Modified Mini-Mental State Examination. The data showed that testing scores were 0.26 units lower among women assigned to conjugated estrogen compared to placebo (P = .04). When the data for estrogen alone was pooled with estrogen plus progesterone, the decrease was 0.21 (P = .006). The adverse effect of hormone therapy was more pronounced in women with low baseline cognitive function. The authors conclude that for women age 65 and older, hormone therapy, including estrogen alone therapy, had an adverse effect on cognition (*JAMA*. 2004;291:2959-2968). As pointed out in the accompanying editorial (*JAMA.* 2004;291:3005-3007), this study did not look at women who took estrogen in the years immediately following menopause. Previous observational data have suggested that there is a critical period just after menopause during which estrogen may be neuro-protective (*JAMA*. 2002;288:2123-2129). However, these current studies seem to conclusively show that neither estrogen nor estrogen plus progesterone are neuroprotective for older women.

Vitamin Therapy and Restenosis

Vitamin therapy to lower homocysteine levels has been touted as an effective way to prevent restenosis after coronary angioplasty. A new study, however, suggests that vitamin combination may actually increase the risk of restenosis in these patients. In a double-blind, placebo-controlled study from Germany and the Netherlands, 636 patients who had undergone successful coronary stenting were randomized to a combination of 1 mg of folic acid, 5 mg of vitamin B, and 1 mg of vitamin B12 intravenously, followed by daily oral doses of the 3 vitamins for 6 months; or to placebo. In a follow-up, the mean luminal diameter was significantly smaller in the vitamin group and placebo group (P = .008), and the extent of luminal loss was greater (P = .004). The restenosis rate was also higher in the vitamin group than the placebo group (34.5% vs 26.5%, P = .05). A higher percentage of patients in the vitamin group also required target vessel revascularization (P = .05). The authors conclude that contrary to previous findings, the administration of folate, vitamin B-6, and vitamin B12 after coronary stenting, may increase the risk of in-stent stenosis (*NEJM*. 2004;350:2673-2681).

Echinacea and the Common Cold

Echinacea purpurea, the commonly prescribed herbal remedy, may have no effect on the common cold, according to a new study. In this randomized, double-blind, placebo-controlled trial, 128 patients with early symptoms of the common cold were randomized to 1 mg of Echinacea or lactose placebo 3 times per day for 14 days or until cold symptoms were resolved, whichever came first. No statistically significant difference was observed between treatment groups for either a total symptom score (P range for symptoms = .29-.90) or mean individual symptom scores (P range = .09-.93). The time toward resolution of symptoms is not statistically significant between the 2 groups (*Arch Intern Med.* 2004;164:1237-1241). The authors admit, however, that testing different preparations and dosing ranges of Echinacea may be needed to confirm these findings.

Effects of Paxil in Children Under 18

GlaxoSmithKline has been accused of suppressing negative data about its antidepressant paroxetine (Paxil), showing that it is broadly ineffective in children and adolescents, and could increase the risk of suicidal behavior. The accusation comes in the form of a lawsuit from New York Attorney General Eliot Spitzer, who filed the suit in early June accusing the company of fraudulently suppressing the data. In response, Glaxo has published several studies on its web site, and states that these studies had previously been published in journals or presented at scientific meetings. The company also reiterates that paroxetine is not approved for treatment of patients 18 years or younger, and states that they do not promote off-label use of their products. The British firm has released data from 9 pediatric trials, as well as the bibliography of public communications derived from the studies, and letters to United States physicians summarizing the data. As mentioned earlier, GlaxoSmithKline, has stated publicly, it's support of the American Medical Association's proposal to create a national registry of all proposed pharmaceutical studies. More information is available at www.gsk.com/media.

FDA Actions

Schering has received approval from the FDA to market a new low dose estrogen patch for the treatment of osteoporosis. The patch, which is dime sized, is applied once a week, and delivers 14 micrograms per day of estradiol. It will be marketed this summer under the trade name Menostar. ■