

Better Sexual Function Follows Body Image Gains

BY DAMIAN McNAMARA

HOLLYWOOD, FLA. — A better body image perception following pelvic organ prolapse treatment correlated with improved sexual function in a multicenter, prospective cohort study of 239 women.

Sexual function improved 4-6 months after treatment compared with baseline, regardless of whether patients had surgery or pessary placement. Sexual function im-

provements also correlated with decreased bother from pelvic organ prolapse.

“Sexual dysfunction is highly prevalent in women attending urogynecology services,” Dr. Lior Lowenstein said at the annual meeting of the American Urogynecologic Society. He estimated this condition affects as many as 60% of sexually active patients.

Other researchers previously demonstrated that women seeking treatment for

advanced pelvic organ prolapse report a worse perception of body image and decreased quality of life, compared with controls who did not have pelvic organ prolapse (Am. J. Obstet. Gynecol. 2006;194:1455-61). The current study was designed to see if treatment improves body image and/or sexual function, and if there is any relationship between these two factors and prolapse symptoms.

Dr. Lowenstein and his colleagues en-

rolled 384 consecutive women presenting for urogynecologic care at one of eight U.S. academic medical centers.

At baseline, the mean prolapse stage was III, and the mean age was 62 years. At 4-6 months’ follow-up, 145 women were lost to follow-up, but there were no significant demographic differences between that group and the 239 women who remained, said Dr. Lowenstein, who was a urogynecology fellow at Loyola University Medical Center in Chicago at the time of the study. He is now an instructor at Rambam Medical Center in Haifa, Israel.

The majority of patients (86%) chose surgery—most commonly sacrocolpopexy. The remainder opted for more conservative treatment with a pessary. A total of 126 women (61%) in the surgery cohort and 22 (67%) in the pessary group said they were sexually active—a not significant difference.

A meeting attendee asked if women treated with pessaries needed to remove them prior to sexual intercourse. “That was not part of the questionnaire we gave them, but it is an important issue that needs to be explored,” Dr. Lowenstein said.

The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire–12 (PISQ-12) was used to assess sexual function. Poorer sexual function, defined by lower scores on the PISQ-12, significantly correlated with worse body image perception. Worse body image perception was reflected by higher scores on the Modified Body Image Perception Scale (MBIS).

Lower PISQ-12 numbers also correlated with significantly more bothersome prolapse—defined by higher scores on the prolapse subscale of the Pelvic Floor Distress Inventory (PFDI). Interestingly, Dr. Lowenstein said, the anatomic site of prolapse did not make a significant difference. The PISQ-12 scores were not significantly related to prolapse stage or apical compartment (anterior, apical, or posterior).

In addition to the three validated questionnaires, the investigators took a patient history, conducted a routine pelvic examination, and determined prolapse stage using the Pelvic Organ Prolapse Quantification (POP-Q) exam at baseline and follow-up. Dr. Lowenstein presented these results on behalf of the Fellows’ Pelvic Research Network. The complete study findings have been published in the Journal of Sexual Medicine (2009;6:2286-91).

“Body image perception has an important role in sexual function in women with pelvic organ prolapse,” Dr. Lowenstein said. He added that the results suggest sexual function may be related more to a woman’s perception of her body image than to actual topographic changes from pelvic organ prolapse.

ACTIVELLA*

(estradiol/norethindrone acetate) tablets
1.0 mg/0.5 mg
0.5 mg/0.1 mg

Rx Only

(For Full Prescribing Information and Patient Information, visit www.activella.com.)

CARDIOVASCULAR AND OTHER RISKS

Estragens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders and Dementia**.) The estrogen plus progestin subcategory of the Women’s Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**.) The estrogen-alone subcategory of the WHI reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders**.) The Women’s Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.) Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE Activella 1.0 mg/0.5 mg and 0.5 mg/0.1 mg are indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.
2. Prevention of postmenopausal osteoporosis. When prescribed solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Activella 1.0 mg/0.5 mg is also indicated in women who have a uterus for the:

3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.
4. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS Activella should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Known hypersensitivity to the ingredients of Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.
8. Known or suspected pregnancy. There is no indication for Activella in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS

See BOXED WARNINGS.

1. **Cardiovascular disorders** Estrogen plus progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism. Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT). Should any of these events occur or be suspected, estrogens should be discontinued immediately. Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or thrombotic disorders (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.
2. **Stroke** In the estrogen plus progestin subcategory of the Women’s Health Initiative (WHI), a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625mg/2.5mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES** in prescribing information.)
3. **Hypertriglyceridemia** In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
4. **Impaired liver function and past history of cholestatic jaundice** Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with prior estrogen use during pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.
5. **Hypothyroidism** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogen may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their thyroid hormone levels in an acceptable range.
6. **Fluid retention** Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this effect, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.
7. **Hypocalcemia** Estrogens should be used with caution in individuals with severe hypocalcemia.
8. **Ovarian cancer** The estrogen plus progestin subcategory of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin versus placebo was 1.58 (95% CI 0.77–3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 2.7 per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in total 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.
9. **Exacerbation of endometriosis** Endometriosis may be exacerbated with administration of estrogens. Malignant transformation of residual endometrial implants has been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.
10. **Exacerbation of other conditions** Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

8. Patient Information Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.

9. Laboratory Tests Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, estrone, estrin).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII, antigen, VIII, coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels by increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay), or T₄ levels by radioimmunoassay; T₄ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), SHBG) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, albumin).
4. Increased plasma HDL and HDL cholesterol subfraction concentration, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metoprolol test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term continuous administration of estrogen with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS**.)

F. Pregnancy Activella should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers Estrogen administration to nursing mothers has been shown to decrease the

estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastases to the brain were more common in the estrogen-plus-progestin group. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% CI 0.62-1.04). In a one-year trial among 1,176 women who received either unopposed 1 mg estradiol or a combination of 1 mg estradiol plus one of three different doses of NETA (0.1, 0.25, and 0.5 mg), seven new cases of breast cancer were diagnosed with local relapse among the group of 295 women treated with Activella 1.0 mg/0.5 mg and two of which occurred among the group of 294 women treated with 1 mg estradiol/0.1 mg NETA.

The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammography results.

Endometrial cancer The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for five to ten years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur in approximately 1% or less with the use of low-dose, continuous, oral estrogen therapy. (See **BOXED WARNINGS**.)

3. Dementia In the estrogen-plus-progestin Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-alone WHIMS substudy, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia (CE vs. placebo) or probable dementia (estrogen plus progestin vs. placebo) (1.21 vs. 0.95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk of probable dementia was 1.49 (95% CI 1.03-2.09). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo. Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE-alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer’s disease.

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ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse effects that appear to be related to drug use and for approximating rates.

Adverse events reported with Activella 1.0 mg/0.5 mg by investigators in the Phase 3 studies regardless of causality assessment are shown in Table 6.

TABLE 6: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA 1.0 MG/0.5 MG

	Endometrial Hyperplasia Study (12-Months)		Vasomotor Symptoms Study (3-Months)		Osteoporosis Study (2 Years)	
	Activella 1.0 mg/0.5 mg (n=295)	1 mg E2 1.0 mg/0.5 mg (n=296)	Activella 1.0 mg/0.5 mg (n=29)	Placebo (n=34)	Activella 1.0 mg/0.5 mg (n=47)	Placebo (n=48)
Body as a Whole						
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
Digestive System						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
Nervous System						
Insomnia	6%	4%	3%	2%	0%	8%
Emotional Lability	1%	1%	0%	0%	6%	0%
Respiratory System						
Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
Metabolic and Nutritional						
Weight increase	0%	0%	0%	0%	9%	6%
Genitourinary System						
Breast Pain	24%	10%	21%	0%	17%	8%
Post-Menopausal Bleeding	5%	15%	10%	3%	11%	0%
Uterine Fibroid	5%	4%	0%	0%	4%	8%
Ovarian Cyst	3%	2%	7%	0%	0%	8%
Resistance mechanism						
Influenza Virus	4%	6%	0%	3%	6%	6%
Morbilli Genital	4%	7%	0%	0%	6%	0%
Secondary Terms						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

*Including one upper extremity fracture in each group. Adverse events reported with Activella 0.5 mg/0.1 mg by investigators during the Phase 3 study regardless of causality assessment are shown in Table 7.

TABLE 7: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA 0.5 MG/0.1 MG

	Activella 0.5 mg/0.1 mg (n=194)	Placebo (n=200)
	Body as a Whole	
Back Pain	10%	14%
Headache	22%	19%
Pain in extremity	5%	4%
Digestive System		
Nausea	5%	4%
Diarrhea	6%	6%
Respiratory System		
Nasopharyngitis	21%	18%
Genitourinary System		
Endometrial thickening	10%	4%
Vaginal hemorrhage	26%	12%

The following adverse reactions have been reported with estrogen and/or progestin therapy:

1. **Genitourinary system** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; premenstrual-like syndrome; cystitis-like syndrome; ovarian cancer; endometrial hyperplasia; endometrial cancer.
2. **Breasts** Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.
3. **Cardiovascular** Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.
4. **Gastrointestinal** Nausea, vomiting, changes in appetite; cholestatic jaundice; abdominal pain/cramps, flatulence, bloating; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.
5. **Skin** Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; seborrhea; hirsutism; itching; skin rash; pruritus.
6. **Eyes** Retinal vascular thrombosis, intolerance to contact lenses.
7. **Central nervous system** Headache; migraine; dizziness; mental depression; chorea; insomnia; nervousness; mood disturbances; irritability; exacerbation of epilepsy; probable dementia.
8. **Miscellaneous** Increase or decrease in weight; aggravation of porphyria; edema; leg cramps; changes in libido; fatigue; reduced carbohydrate tolerance; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; back pain; arthralgia; myalgia.

OVERDOSAGE

Serious effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdose of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Activella is administered to a nursing mother.

H. Pediatric Use Activella is not indicated in children.

I. Geriatric Use Clinical studies of Activella did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

Of the total number of subjects in the estrogen-plus-progestin subcategory of the Women’s Health Initiative (WHI) study, 44% (n=7,320) were 65-74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 hysterectomized women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% CI 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-alone substudy of WHI, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over. In the estrogen-alone WHIMS substudy, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE-alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer’s disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk of probable dementia was 1.49 (95% CI 1.03-2.09). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo. Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE-alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer’s disease.

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