

Appendix E: Hormonal Replacement Therapy Regimens E

The proportion of post-menopausal women who use hormone replacement therapy (HRT) has increased in the United States during the last two decades (13). While use of HRT has increased, the average dose and duration of use of postmenopausal estrogens has decreased until recently (64). This is due in part to the discovery that the cancer-causing effects of postmenopausal estrogen are related to its dose and duration.

This appendix describes the range of choice regarding the dose, routes of administration, and combinations of hormones currently in use or under study as treatment for postmenopausal HRT. This appendix also describes the appropriate follow-up of women on HRT. Finally, this appendix describes how dosing regimens may affect compliance with HRT and describes other factors that affect HRT compliance.

HRT involves the administration of estrogen alone or in combination with progestins. In the past, estrogen was typically administered without progestin (unopposed estrogen) in estrogen replacement therapy (ERT). Currently, the most commonly used regimens for a woman with a uterus include a progestin either in sequence with estrogen (e.g., 25 days of estrogens with a concurrent progestin administered during the last 12 to

14 days and a three-day drug-free period) or in continuous combination with estrogen. These progestin/estrogen therapies (PERTs) alter the benefit-risk profile of HRT.

In the United States, conjugated equine estrogen (CEE) (Premarin, Wyeth-Ayerst) is the most commonly used form of estrogen for HRT.^{1,2} There are a number of other estrogens used for HRT.³ Table E-1 lists the estrogens either approved for osteoporosis by the Food and Drug Administration or accepted for this use by a committee of the United States Pharmacopoeia. In addition to the estrogens listed in the table, the estrogens quinestrol (Estrovis tablets, Parke-Davis) and chlorotrianisene (TACE capsules, Marion Merrel Dow) are approved by the FDA for treatment of menopausal symptoms (61).

ESTROGEN DOSING REGIMENS

A central question for clinical management of postmenopausal HRT patients is how small a dose of estrogen may be administered without losing the beneficial effects of the therapy. The reduction in bone loss or menopausal symptoms must be weighed against the adverse effects of estrogens. The higher the dose of estrogen, the more likely are side effects, such as breast tenderness or fluid

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retention (15, 27, 28).⁴ In addition, higher doses may increase the risk of estrogen-related illness such as endometrial cancer or gallbladder disease.

Several studies have demonstrated that doses of at least 0.625 mg per day of CEE or its equivalent are necessary to prevent or greatly reduce bone loss in the spine in peri- or postmenopausal women (36,46,72). Lower doses offer only partial protection against bone loss (46,47). The minimal dosage of estrogen adequate to prevent bone loss in postmenopausal women is discussed in greater detail in appendix C.

The American College of Obstetricians and Gynecologists recommends the following estrogen dosages for osteoporosis (1):

Estrogen	Dose
conjugated estrogen	0.625 mg/day
transdermal estradiol	0.05 mg twice a week
micronized estradiol	1.0 mg/day
estrone sulfate	1.25 mg/day

For women who have not had hysterectomies, ACOG recommends the addition of a progestin to the estrogen. They recommend a dose of 10 mg/day for 12 days a month to reduce the incidence of hyperplasia and endometrial cancer. ACOG and the American College of Physicians see no reason to add progestin to estrogen for a woman without a uterus.

■ Routes of Administration

There are a number of routes for delivery of estrogens other than by mouth. Intramuscular injections have been tested, but they are no longer used, not only because they are uncomfortable but also because estrogen plasma concentrations are unstable with this method of administration (68). Vaginal rings and vaginal creams have also been investigated (53,63), but plasma estrogen levels are unstable, probably because of irregular ab-

¹There are currently no generic forms of conjugated estrogens on the market, but there are generic forms of some of the other estrogens used for postmenopausal replacement therapy. In 1989, the Center for Drug Evaluation and Research of the FDA rejected applications for new drug approval submitted by Barr Laboratories for five dosage strengths of generic conjugated estrogen (7). Although the extent of absorption of the estrogen was the same as that of Premarin, the brand-name drug manufactured by Wyeth-Ayerst, the FDA ruled that the generic manufacturer must demonstrate that the *rate* of absorption must be the same in order for the generic products to be considered bioequivalent to the innovator drug. Barr Labs claimed that this was inconsistent with a January 1989 determination by the FDA's Fertility and Maternal Health Drugs Advisory Committee that the rate of absorption was not relevant to bioequivalence (7).

Although a few members acknowledged that there was no conclusive evidence that the rate of estrogen absorption is important in determining the safety and efficacy of conjugated estrogens, the FDA's Generic Drugs Advisory Committee concluded in February 1991 that the rates of absorption must be the same to establish bioequivalence (16). The FDA contended that different absorption rates could make conjugated estrogens ineffective in treating osteoporosis. In addition, more rapid absorption of estrogen into the blood stream could lead to higher peak drug plasma concentrations which could increase the risk of endometrial cancer (30).

At present, sponsors of generic conjugated estrogen products are required to perform studies of the blood concentration-time profiles of five of the predominant estrogens in Premarin brand of conjugated equine estrogen (4). As of 1995, there were no generic conjugated estrogens on the market, although the generic manufacturer Duramed had an ANDA pending for a 0.625 mg formulation (4). Wyeth-Ayerst, manufacturer of Premarin brand of conjugated estrogen, has argued that a conjugated estrogen product that does not also contain a sixth form of estrogen, delta(8,9)-dehydroestrone, is not substantially equivalent to Premarin.

² Data from Wyeth-Ayerst, manufacturers of the most widely prescribed postmenopausal estrogen, show that three types of physician specialists — obstetrician-gynecologists, internists, and family-practitioners — wrote 90 percent of estrogen prescriptions. Obstetrician-gynecologists prescribe the most, with 2,897,000 prescriptions, or 43 percent of prescriptions for postmenopausal estrogens.

³ The estrogens used in hormone replacement therapy are much less potent than the synthetic estrogens used in oral contraceptives. Because of this difference in potency, the side effect profile of estrogens used in hormonal replacement therapy differs from that of estrogens used for contraception.

⁴ Fibroid tumors and endometriosis may also be exacerbated by HRT. Fibroids and endometriosis are both estrogen-dependent conditions that regress at menopause. HRT in postmenopausal women who had significant problems from either of these diseases premenopausally requires careful surveillance: fibroids may enlarge, and endometriosis maybe reactivated. If HRT is subsequently discontinued, the fibroids will again shrink. However, the sequelae of endometriosis, such as chocolate cysts or adhesions, may persist even after estrogen has been withdrawn, and continue to cause symptoms (20).

TABLE E-1: Estrogen Products Available in the U.S. for Osteoporosis (Page 1 of 2)

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and/or menopausal symptoms ^{a,b}
Conjugated equine estrogen	Premarin tablets	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vaginal or urethral atrophy 3) Osteoporosis 4) Hypoestrogenism due to castration, hypogonadism, or primary ovarian failure 5) Breast cancer 6) Prostatic carcinoma	Menopausal symptoms: 0.625 mg to 1.25 mg a day cyclically or continuously Osteoporosis: 0.3 mg to 1.25 mg a day, cyclically or continuously
Diethylstilbestrol (DES) ^c	Diethylstilbestrol enteric-coated tablets ^d Diethylstilbestrol tablets ^d	Lilly	1) Breast cancer 2) Prostatic carcinoma	Neither the USP DI nor the product labeling includes dosage information for osteoporosis or menopausal symptoms.
Esterified estrogens	Estratab tablets Menest tablet	Solvay SmithKline Beecham	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar or vaginal atrophy 3) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure 4) Breast cancer 5) Prostatic carcinoma	Menopausal symptoms: 0.625 mg to 1.25 mg, cyclically or continuously
Estradiol	Estrace tablets Emcyt capsules	Bristol-Myers Squibb Pharmacia Adria	1) Osteoporosis 2) Moderate to severe vasomotor symptoms of menopause 3) Vulvar or vaginal atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure 5) Breast cancer 6) Prostatic carcinoma	Menopausal symptoms: 0.5 mg to 2 mg a day, cyclically or continuously Osteoporosis: 0.5 mg a day, cyclically or continuously

TABLE E-1: Estrogen Products Available in the U.S. for Osteoporosis (Page 2 of 2)

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and/or menopausal symptoms ^{a,b}
Estradiol transdermal system	Estraderm	Ciba	1) Osteoporosis 2) Moderate to severe vasomotor symptoms of menopause 3) Vulvar or vaginal atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	Osteoporosis or menopausal symptoms: One transdermal dosage system delivering 0.05 mg or 0.10 mg, per day worn continuously and replaced twice a week
Estropipate	Ogen tablets	Upjohn	1) Osteoporosis ^c 2) Moderate to severe vasomotor symptoms of menopause	Menopausal symptoms: 0.75 mg to 5 mg estropipate per day, cyclically or continuously
	Ortho-est tablets	Ortho	3) Vaginal or vulvar atrophy 4) Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure	Osteoporosis: 0.75 mg per day for 25 days of a 31-day cycle
Ethinyl estradiol ^d	Estinyl tablets	Schering	1) Moderate to severe vasomotor symptoms of menopause 2) Hypogonadism 3) Prostatic carcinoma 4) Breast cancer	Menopausal symptoms: 0.02 mg of 0.05 mg per day, cyclically or continuously

^aDosages are for vasomotor symptoms of menopause.

^bDosages were those recommended in the USP DI, See the United States Pharmacopeial Convention, *USP Dispensing Information (USP DI): Volume 1—Drug Information for the Health Care Profession* (Taunton, MA Randy McNally, 1995).

^cA U.S. Pharmacopeia Advisory Committee has accepted osteoporosis as an unlabeled indication for this product. An indication for postmenopausal osteoporosis, however, is not included in the FDA-approved labeling for this product See The United States Pharmacopeial Convention, *USP Dispensing Information (USP DI): Volume 1—Drug Information for the Health Care Profession* (Taunton, MA Rand McNally, 1995).

^dDiethylstilbestrol is available only as a generic in the United States.

^eThe FDA-approved labeling of Ortho-est (Ortho) brand of estropipate does not include an indication for osteoporosis

Key: CEE = conjugated equine estrogen, HRT = hormone replacement therapy, t m = trademark

SOURCE: Office of Technology Assessment, 1995

sorption due to day-to-day changes in vaginal blood flow and secretion.

Implantation of continuously released estrogen under the skin (subcutaneous implantation) appears to result in stable estrogen levels (68). But once inserted, the implants are difficult to remove in case of overdose or intolerance (76).

Administration of estrogen through a patch or cream applied to the skin (percutaneous transdermal administration) has proved effective in treating postmenopausal symptoms (14,22) and in reducing vertebral bone loss after menopause (72).

Transdermal medication may increase compliance because it eliminates the need for multiple dose scheduling, is easily administered, requires only twice weekly application, and is reversible (78). However, the gel is difficult to administer accurately (68). Absorption is proportional to the surface of application, and this surface cannot be determined accurately. In addition, between 5 and 20 percent of women may develop skin irritation (79).

THERAPY WITH PERT

The primary indication for adding progestins to estrogen replacement therapy is to reduce the risk of estrogen-induced irregular bleeding, endometrial hyperplasia (abnormal overgrowth of the inner lining of the uterus, or endometrium), and endometrial cancer (26,87). (See appendix G.) In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, almost half of the women assigned to unopposed estrogen therapy experienced endometrial hyperplasia over the two year clinical trial (91); the PEPI trial protocol required that these women be taken off of estrogen. Because of the unexpectedly large proportion of women on ERT who developed hyperplasia in PEPI, the directors of the Women's Health Initiative long-term clinical trial of hormonal replacement therapy decided to place all women assigned to unopposed estrogen on PERT.

A number of progestins can be used for PERT.⁵ The most commonly used progestin in the United States is medroxyprogesterone (Provera, Upjohn). In addition, the FDA has recently approved a combination of medroxyprogesterone acetate and conjugated equine estrogen for the prevention of osteoporosis. (See table E-2.)

Progestins produce progressive endometrial atrophy, converting adenomatous hyperplasia to normal endometrium (85). Numerous studies show that combined estrogen/progestin therapies can return 98 to 99 percent of preexisting hyperplasia back to normal endometrium (32,73). (See appendix G.) Observational studies also show that PERT users have a lower risk of endometrial cancer than ERT users (42).

An important unresolved issue regarding PERT is whether the benefits of progestins in protecting the endometrium are outweighed by the effect of progestins on the risk of coronary heart disease (CHD). Epidemiologic studies of the relationship of HRT to CHD have been largely limited to unopposed estrogens; the effect of progestin supplementation on heart disease risk has not been as extensively evaluated, but recent evidence suggests that adding progestins to HRT may attenuate the beneficial effects of ERT on heart disease. (See appendix I.)

Progestins are more often responsible than estrogen for making hormonal replacement therapy unacceptable for some women, because adverse effects are common with progestins (71). Progestins can produce breast tenderness, bloatedness, edema, abdominal cramps, and an iatrogenic premenstrual-like syndrome (71,87). Patients also commonly experience side effects such as anxiety, irritability, depressed mood, and drowsiness.

One of the primary reasons for stopping HRT is discomfort with periodic bleeding (18). With sequential therapies, regular bleeding occurs with 85 percent of patients (31,87). This proportion decreases with time, and by age 65, 60 percent continue to experience light bleeding (33). Patients

⁵ Synthetic Progesterone are often used in hormonal replacement therapy since natural progesterones cannot be absorbed orally.

TABLE E-2: Progestins Products Available in the U.S. for Use with Estrogen in Osteoporosis^a

Generic name	Brand name (tin.)	Manufacturer	FDA-approved indications	Recommended dosage for secondary amenorrhea ^b
Medroxyprogesterone acetate	Amen	Carnick	1) Secondary amenorrhea	Secondary amenorrhea. May be given in dosages of 5 to 10 mg daily for from 5 to 10 days.
	Curretab	Solvay	2) Abnormal uterine bleeding	
	Cycrin	Esi Pharma		
	Provera	Upjohn		
Norethindrone acetate	Aygestin	Esi Pharma	1) Secondary amenorrhea	Secondary amenorrhea: May be given in dosages of 2.5 to 10 mg daily for 5 to 10 days during the second-half of the theoretical menstrual cycle.
	Norlutate	Parke-Davis	2) Endometriosis	
			3) Abnormal uterine bleeding	

^a A U.S. Pharmacopeia Advisory Committee has determined that osteoporosis is an accepted indication for these products. An indication for osteoporosis, however, is not included on the FDA-approved labeling for these products. See The United States Pharmacopeial Convention's *Dispensing Information (USP DI): Volume 1—Drug Information for the Health Care Profession* (Tauton, MA: Rand McNally, 1995).

^b The FDA-approved product labeling does not have dosage recommendations for use of these products with estrogen in Osteoporosis.

KEY: t.m. = trademark

SOURCE Office of Technology Assessment, 1995

may be willing to tolerate bleeding for relief of menopausal symptoms, but to an asymptomatic woman in her 60s and 70s who is taking estrogens for the prevention of osteoporosis and cardiovascular disease, the persistent bleeding and other side effects may be intolerable (26).

Compliance may be improved with new continuous combined regimens of PERT that reduce the frequency of menstrual bleeding. Continuous PERT involves daily administration of estrogen and a low dose of progestin (70). Several studies show that continuous PERT can relieve menopausal symptoms, eliminate periodic bleeding within several months of initiation, and avoid endometrial hyperplasia (5,28,37,40,48,70,84,91).

Most studies to date have found between one-third and one-half of patients were bleeding after three months of continuous PERT, but most patients were amenorrheic after 12 months. And most studies reported 90 percent or greater atrophic endometrium at 12 months.

Another approach to reduce the frequency of bleeding and improve compliance is to give sequential PERT with less than monthly progestin therapy. For example, Williams and colleagues found that there was less vaginal bleeding when progestins were administered for 14 days every three months than when given for 14 days every month (90). Menopausal women find less than monthly bleeding more acceptable than monthly bleeding (6).

ACUTE INDICATIONS FOR HRT

The most common indication for HRT is relief of menopausal symptoms (41).⁶ Hot flashes, or vasomotor symptoms, are the most common symptom of menopause that causes women to seek medical attention (81). Hot flashes occur in 60 to 75 percent of women at the time of menopause (52,82). They are typically more severe in women with surgical menopause, because the severity of

⁶ The American College of Physicians distinguishes between diagnoses for short-term and long-term HRT (3). Short-term HRT is prescribed for women who suffer from postmenopausal symptoms, such as hot flashes and atrophic vaginitis. The American College of Physicians suggests therapy of one to five years for the treatment of symptoms associated with menopause. The goals of long-term HRT are the prevention of osteoporosis and decrease in the risk of heart disease. The American College of Obstetricians and Gynecologists recommends that for treatment of menopausal symptoms, the lowest dosage of estrogen that provides effective relief should be used (1).

vasomotor symptoms is thought to be related to the rapidity in decline of estrogen (51). At first, flashes usually occur several times a day, and often interrupt sleep (25). Irritability, fatigue, and anxiety can result from sleep deprivation. For most patients, vasomotor symptoms are self-limiting, but for 25 to 50 percent of women, these flashes persist more than five years (77,82). Clinical trials have demonstrated that estrogen is effective in relieving these symptoms in about 95 percent of patients (19,75).

Estrogen has been found to relieve symptoms of menopause that affect the vagina, uterus, urethra, and bladder.⁷ Estrogen replacement therapy can prevent the vaginal atrophy associated with menopause and maintain the normal tone of supporting ligaments and elastic tissues of the uterus and vagina (9,80,89). Vaginal atrophy may result in vaginal dryness, itching, burning, and infection. Vaginal atrophy can also result in pain with vaginal intercourse and resultant sexual dysfunction (10). Estrogen can also prevent atrophy of the bladder and urethra and the resultant painful urination, urgency, stress incontinence, frequency of urination, urination at night, and dripping after voiding (24,29,66,80).

The absence of estrogen may cause skin to become thinner, as the amount of collagen in the skin decreases (10,80). Estrogen stimulates the synthesis of collagen, and in postmenopausal women receiving estrogen, the collagen of the skin is maintained at premenopausal levels (11).

Some investigators have shown reductions in anxiety and depressed mood, and improvements

in feelings of well being in women on HRT (21,56,88,89). This effect may be independent from its impact on menopausal symptoms (45).⁸

EVALUATION AND FOLLOWUP OF WOMEN TAKING HRT

Before hormonal replacement therapy is begun by a postmenopausal woman, the American College of Physicians (ACP) recommends that her physical condition should be assessed by a physician (3). The doctor should be aware of her medical history and her current health in light of contraindications to HRT. These contraindications include unexplained vaginal bleeding, acute liver disease, chronic impaired liver function, recent vascular thrombosis, breast cancer, and endometrial cancer.

The American College of Obstetricians and Gynecologists (ACOG) recommends that women taking hormonal replacement therapy be monitored every year (1). At that time breast and pelvic examinations should be performed, a Pap smear should be taken, and cholesterol level and blood pressure should be monitored. If the woman is on a regime that includes a progestin and there is no excess or prolonged bleeding, there is no need for an annual endometrial biopsy. Mammograms should be performed annually on women over the age of 50.

Endometrial biopsy is not deemed to be necessary in patients on sequential PERT because the onset of bleeding can be a useful predictor of endometrial status. Patients with proliferation and

⁷ Alternatives to estrogen, such as progestogens, clonidine, or ergot alkaloids, have been used for symptomatic relief of vasomotor symptoms in women who are not candidates for estrogen replacement therapy (75,81). But none of these alternatives will prevent atrophy of the vagina (81).

⁸ A major difference of opinion persists as to whether estrogen therapy has any direct positive effect on mood, or whether the improved well-being reported by some women is simply due to their relief from vasomotor symptoms, and possibly due to a placebo effect (60). Some studies purport to show that a large portion of the influence of hormone replacement on affect is due to alleviation of hot flashes by hormone replacement (23). Yet other studies have demonstrated that estrogen therapy directly affects mood (12). Campbell and Whitehead, in a double-blind study of 64 women over four months, demonstrated significant improvements in certain psychological problems such as anxiety, irritability, worry about age, and optimism. They found that estrogen significantly improves anxiety and other psychological symptoms even in menopausal women who had had no vasomotor symptoms. However, a direct biological effect of loss of estrogen with menopause on depressed mood has not been demonstrated (35). Although estrogen may help alleviate depressed mood that accompanies menopause (44), major depression requires psychiatric treatment (35).

hyperplasia of the endometrium bleed earlier in the cycle than is normal with sequential PERT (59,87).

COMPLIANCE WITH HRT

A number of studies that have examined rates of compliance with HRT have in general found long-term compliance rates to be low. One study of 1,586 women enrolled in the Harvard Community Health Plan who received new prescriptions for HRT found that 27 percent stopped taking HRT within 100 days of receiving the prescription and 40 percent had stopped after one year (50).

Some studies distinguish between commencement compliance (the proportion of women prescribed HRT who initiate therapy) and maintenance compliance (proportion of women on HRT who continue to take it over a specified period of time). Speroff et al. (1991) estimated that the commencement compliance rate for women with natural menopause is between 21 and 60 percent (69). The five-year maintenance compliance rate is between 5 and 34 percent. For women with bilateral oophorectomies, the commencement compliance rate is between 31 and 89 percent. Their five-year maintenance rate is 13 to 71 percent (69).

Compliance with HRT tends to decrease over time. One study conducted for Wyeth Ayerst examined compliance with HRT in postmenopausal women who were members of a prepaid group health benefit plan and who filled prescriptions for conjugated equine estrogens (Premarin, Wyeth Ayerst) (83). Data on rates of compliance were gathered from pharmacy and medical records. Compliance rates were determined by comparing the number of days Premarin was prescribed to the number of days for which Premarin was dispensed. They found that compliance declined from 62.7 percent over one year, to 56.1 percent over three years and to 46.8 percent over seven years.

Compliance with HRT is affected by various factors, and knowledge of these factors suggests ways of improving compliance. In addition, knowledge of these factors is important in understanding how bias may affect our interpretation of observational studies of HRT's risks and benefits. (See appendices F and I for a discussion of bias.)

In general, compliance rates with drugs will be lower if the patient suffers no physical symptoms or if the symptoms disappear before the end of the treatment (62). Women who suffer from more severe menopausal symptoms, such as hot flashes, are more likely to use hormone replacement therapy. It has been found that women with surgical menopause are more likely to use and comply with long-term hormone replacement therapy, in part because their menopausal symptoms tend to be more severe (13,43). Leaner women are more likely to use hormonal replacement therapy; because body fat is an important nonovarian source of estrogen production, thin women tend to have more severe menopausal symptoms than women who are heavier (34). Women who smoke cigarettes are more likely to take HRT, possibly because of an antiestrogenic effect of smoking, which intensifies menopausal symptoms (38). But the proportion of women who use HRT for relief of acute menopausal symptoms declines in the years following menopause as these symptoms diminish in frequency and severity.

Women typically do not suffer symptoms of osteoporosis, such as hip fractures or kyphosis, until many years after menopause. Because low bone mineral density (BMD) does not have obvious symptoms unless fracture occurs, bone density measurement may increase commencement and maintenance compliance with HRT. Some experts have suggested physicians could use densitometry to help patients who are undecided about initiating HRT to "visualize" their low bone mass (57).⁹ In addition, maintenance compliance might

⁹ Measurements of biochemical markers of bone resorption may also be used to improve compliance with HRT. These markers may allow the clinician to identify patients who are failing to respond to HRT, which may be because the patient is not complying with the prescribed regimen (41a). The use of biochemical markers of bone resorption as a tool to improve compliance with HRT has not been evaluated (Id.).

be improved by using densitometry to follow a patient's bone density over time, although there is no evidence available to test this possibility.

Women with below-normal BMD as determined by densitometry are more likely to take estrogen as a preventive measure for osteoporosis (65). One study surveyed 261 women in California who had had their BMD measured. Postmenopausal women who had below-average BMD for their age, sex, and race combination were five times as likely to begin taking estrogen as women with normal densitometry results (odds ratio 8.4, 95 percent confidence interval 3.4 to 20.9). While the study showed that more women with low BMD at densitometry initiated estrogen replacement therapy than women with normal BMD, it did not report on the effect of densitometry on long-term compliance with HRT. Another study of compliance with HRT among 352 postmenopausal women who had BMD measurements, however, found that 40 percent of the women who were recommended HRT for low bone density were not taking HRT eight months after referral (67).

Women's attitudes and beliefs about HRT affect compliance with hormonal replacement therapy. In general, compliance with drugs will be lower if the patient is not convinced the medication will help or if the patient is afraid of the development of side effects (62). Many women are resistant to taking HRT because it is "not natural" (54). Women may discontinue HRT because of unacceptable side effects, such as resumed menstruation, breast tenderness, weight gain, headaches, and abdominal bloating (55). In addition, women may decide not to use HRT because it may increase their risk of endometrial cancer and breast cancer.

Greater patient education about the magnitude and direction of effects and risks may improve compliance with HRT. In general, compliance is better with more patient education about the disease and the regimen (55).

The uptake and compliance with HRT may also be affected by physicians' beliefs and recommendations. A number of factors appear to influence

physicians in their prescribing of HRT, including estimates of benefits and risks that may not be supported by scientific data (74). In addition, some physicians appear to use patterns of administration of HRT that may diminish the chance of appropriate patient compliance and fail to adjust therapy when problems occur (74).

The clinical setting may also have an impact on compliance. Experimental clinical trials of HRT have generally shown better rates of compliance than studies of HRT compliance outside of the trial setting. For example, one clinical trial of HRT in women with hysterectomies showed perfect compliance during the 18 months of the study (39). A clinical trial of estrogen patches showed perfect compliance over four months (58). Both of these clinical trials involved small samples of women (22 and 12, respectively.) In addition, compliance may be better in clinical trials because there are more intensive efforts at follow-up than generally occur in the normal clinical settings.

Compliance is also affected by the age at which hormonal replacement therapy is initiated. Elderly postmenopausal women more frequently object to the resumption of menstrual bleeding induced by PERT than perimenopausal and early postmenopausal women (6). Other factors also affect the compliance of elderly patients with medication regimens. A patient is less likely to comply if she has a poor understanding of the prescription instructions, if the therapy is long term, or if the prescription has complex instructions (62). An elderly woman may suffer from impaired vision or hearing that could impede her ability to read a drug label or hear instructions for its use. In addition, many elderly people live alone, and it has been shown that people who live alone are less likely to comply with a medication regimen than those who do not (62). In addition, the expense of certain medications may have an impact on compliance by the elderly with limited fixed incomes.

Behavioral patterns of women who take estrogen, such as regular physician visits (to refill prescriptions, for example), differentiate them from women who do not take estrogen. In order to examine the effect of health behaviors on HRT use,

TABLE E-3: Combination Estrogen/Progestin Products for Osteoporosis in the U.S.

Generic name	Brand name (t.m.)	Manufacturer	FDA-approved indications	Recommended dosages for osteoporosis and menopausal symptoms
Conjugated estrogens and medroxyprogesterone acetate for continuous HRT	Prempro	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar and vaginal atrophy 3) Osteoporosis (in women with an intact uterus)	Menopausal symptoms. 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate daily Osteoporosis: 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate daily
Conjugated estrogens and medroxyprogesterone acetate for sequential HRT	Premphase	Wyeth-Ayerst	1) Moderate to severe vasomotor symptoms of menopause 2) Vulvar or vaginal atrophy 3) Osteoporosis (in women with an intact uterus)	Menopausal symptoms. 0.625 mg CEE (cyclic administration) and 5 mg medroxyprogesterone acetate for last two weeks of cycle Osteoporosis: 0.625 mg CEE (cyclic administration) and 5 mg medroxyprogesterone acetate for last two weeks of cycle

KEY: CEE = conjugated equine estrogen, HRT = hormone replacement therapy, t m = trademark

SOURCE: Office of Technology Assessment, 1995

Barrett-Connor et al. studied 1,057 postmenopausal women from the same socioeconomically upper-middle-class community in California who participated in a clinic evaluation of their estrogen use patterns (8). After an average of 4.4 years later, 95 percent of these women completed a mailed health survey questionnaire. This questionnaire asked them about recent changes in lifestyle behaviors that affect their health, such as consumption of dietary fat, salt use, and exercise habits, as well as frequency of blood pressure checkups, mammograms, and Pap smears.

The study found that women who were currently using HRT were significantly more likely to have recently implemented new healthy lifestyle behaviors than women who had never used HRT (8). For example, 70 percent of the women who were currently using HRT had had a mammogram in the last year, whereas only 45 percent of the women who had never used HRT had had one. Thirty-eight percent of current users had increased

their daily exercise over the past year, whereas only 29 percent of never users had increased their exercise. Women who never used HRT were less likely to have implemented healthy behavior changes, and were least likely to have had screening evaluations than women who had used HRT.

Compliance may be affected by the type of packaging. One study of 177 patients compared a calendar-oriented system of HRT packaging to conventional packaging of HRT (50). Compliance rose from 23 percent when the pills were provided in conventional packaging to 82 percent when the pills were provided in a prepackaged blister card system. Wyeth-Ayerst introduced a prepackaged blister card system of packaging in 1995. (See table E-3.)

Thus, a variety of factors affect compliance with HRT. Increased awareness of the factors affecting compliance with HRT suggests ways of improving long-term compliance.

REFERENCES

1. American College of Obstetricians and Gynecologists, "Hormone Replacement Therapy," *ACOG Technical Bulletin*, No. 166 (Washington, DC: American College of Obstetricians and Gynecologists, April 1992).
2. American College of Obstetricians and Gynecologists, "Osteoporosis," *ACOG Technical Bulletin*, No. 167 (Washington, DC: American College of Obstetricians and Gynecologists, May 1992).
3. American College of Physicians, "Preventive Care Guidelines: 1991," *Annals of Internal Medicine* 114(9):758-783, 1991.
4. "APhA Weighs in on Oestrogens," *Scrip World Pharmaceutical News* 2013:29, 1995.
5. Archer, D. F., Pickar, J. H., and Bottiglioni, F., "Bleeding Patterns in Postmenopausal Women Taking Continuous Combined or Sequential Regimens of Conjugated Estrogens with Medroxyprogesterone Acetate," *Obstetrics & Gynecology* 83(5 Pt 1):686-692, 1994.
6. Barensten, R., Groenvelde, F. P., Bareman, F. P., et al., "Women's Opinion on Withdrawal Bleeding with Hormone Replacement Therapy," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 51(3): 203-207, 1993.
7. "Barr Labs Requests Conjugated Estrogens Hearing to Review FDA's Denial of Blood Level-Based ANDA Applications; Agency Cites Difference in Absorption," *F-D-C Reports* Dec. 4, 1989, pp. 8-10.
8. Barrett-Connor, E., "Postmenopausal Estrogen and Prevention Bias," *Annals of Internal Medicine* 115(6):455-456, 1991.
9. Beard, M. K., "Atrophic Vaginitis. Can It be Prevented as Well as Treated?" *Postgraduate Medicine* 91(6):257-260, 1992.
10. Booher, D.L., "Estrogen Supplements in the Menopause," *Cleveland Clinic Journal of Medicine* 57:154-160, 1990.
11. Brincat, M., Moniz, C.F., Studd, J.W.W., et al., "The Long Term Effects of the Menopause and of Administration of Sex Hormones on Skin Collagen and Skin Thickness," *British Journal of Obstetrics and Gynecology* 92:256-259, 1985.
12. Campbell, S., and Whitehead, M., "Oestrogen Therapy and the Menopause Syndrome," *The Menopause: Clinics in Obstetrics and Gynecology*, Greenblatt and Studds (eds.) (London, England: W.B. Saunders, 1977).
13. Cauley, J. A., Cummings, S.R., Black, D. M., et al., "Prevalence and Determinants of Estrogen Replacement Therapy in Elderly Women," *American Journal of Obstetrics and Gynecology* 163: 1438-1444, 1990.
14. Chetkowski, R., Meldrum, D., Steingold, K., et al., "Biologic Effects of Transdermal Estradiol," *New England Journal of Medicine* 314:1615-1620, 1986.
15. Christensen, M. S., Hagen, C., Christiansen, C., et al., "Dose-Response Evaluation of Cyclic Estrogen/Gestagen in Postmenopausal Women: Placebo-Controlled Trial of Its Gynecologic and Metabolic Actions," *American Journal of Obstetrics and Gynecology* 144(8):873-879, 1982.
16. "Conjugated Estrogens Rate of Absorption Should be Measured—FDA Advisory Committee; New Generic Formulations Could Take at Least Two Years to Develop," *F-D-C Reports* Mar. 4, 1991, pp. 9-10.
17. Coope, J., "Menopause: Diagnosis and Treatment," *British Medical Journal* 289(6449): 888-890, 1984.
18. Coope, J., and Marsh, J., "Can We Improve Compliance with Long-Term HRT?" *Maturitas* 15(2):151-158, 1992.
19. Coope, J., Thomson, J. M., and Poller, L., "Effects of 'Natural Oestrogen' Replacement Therapy on Menopausal Symptoms and Blood Clotting," *British Medical Journal* 4(5989):139-143, 1975.
20. Cust, M., Gangar, K., Hillard, T., et al., "A Risk-Benefit Assessment of Estrogen Therapy in Postmenopausal Women," *Drug Safety* 5:345-358, 1990.
21. Daly, E., Gray, A., Barlow, D., et al., "Measuring the Impact of Menopausal Symptoms

- on Quality of Life," *British Medical Journal* 307(6916):1420-1421, 1993.
22. De Ligni'eres, B., Basdevant, A., Thomas, G., et al., "Biological Effects of Estradiol 17-beta in Post Menopausal Women: Oral Versus Percutaneous Administration," *Journal of Clinical Endocrinology and Metabolism* 62:536-541, 1986.
 23. Dennerstein, L., Burrows, G. C., Hyman, G.J., et al., "Hormone Therapy and Affects," *Maturitas* 1(4):247-259, 1979.
 24. Elia, G., and Bergamn, A., "Estrogen Effects on the Urethra: Beneficial Effects in Women with Genuine Stress Incontinence," *Obstetrical and Gynecological Survey* 48(7): 509-517, 1993.
 25. Erlick, Y., Tataryn, I. V., Meldrum, D. R., et al., "Association of Waking Episodes with Menopausal Hot Flushes," *Journal of the American Medical Association* 245(17): 1741-1744, 1981.
 26. Ernster, V., Bush, T., Huggins, G., et al., "Benefits and Risks of Menopausal Estrogen and/or Progestin Hormone Use," *Preventive Medicine* 17:201-233, 1988.
 27. Ettinger, B., Genant, H., and Cann, C., "Long-Term Estrogen Replacement Therapy Prevents Bone Loss and Fractures," *Annals of Internal Medicine* 102:319-324, 1985.
 28. Ettinger, B., Golditch, I., and Friedman, G., "Gynecologic Consequences of Long-Term Unopposed Estrogen Replacement Therapy," *Maturitas* 10:271-282, 1988.
 29. Fantl, J. A., Cardozo, L., and McClish, D. K., "Estrogen Therapy in the Management of Urinary Incontinence in Postmenopausal Women: A Meta-Analysis. First Report of the Hormones and Urogenital Therapy Committee," *Obstetrics & Gynecology* 83(1):12-18, 1994.
 30. "FDA Position on Conjugated Estrogens Rate of Absorption in Determining Bioequivalence Supported in Split Decision by FDA Advisory Subcommittee," *F-D-C Reports*, May 7, 1990, pp. 7-10.
 31. Fraser, I., "A Review of the Role of Progestins in Hormonal Replacement Therapy: Influence on Bleeding Patterns," *Maturitas* 8:113-121, 1986.
 32. Gambrell, R., "Prevention of Endometrial Cancer with Progestogens," *Maturitas* 8: 159-168, 1986.
 33. Gambrell, R., Bagnell, C., and Greenblatt, R., "Role of Estrogens and Progesterone in the Etiology and Prevention of Endometrial Cancer" (review), *American Journal of Obstetrics and Gynecology* 146:696-707, 1983.
 34. Garcia Rodriguez, L. A., Pfaff, G. M., Schumacher, M. C., et al., "Replacement Estrogen Use and Body Mass Index," *Epidemiology* 1:219-223, 1990.
 35. Gath, D., and Iles, S., "Depression and the Menopause," *British Medical Journal* 300(6735):1287-1288, 1990.
 36. Genant, H., Baylink, D., and Gallagher, J., "Effect of Estrone Sulfate on Postmenopausal Bone Loss," *Obstetrics & Gynecology* 76(4): 579-584, 1990.
 37. Gillet, J. Y., Andre, G., Faguer, B., et al., "Induction of Amenorrhea During Hormone Replacement Therapy: Optimal Micronized Progesterone Dose. A Multicenter Study," *Maturitas* 19(2): 103-115, 1994.
 38. Greenberg, G., Thompson, S. G., and Meade, T.W., "Relation Between Cigarette Smoking and Use of Hormonal Replacement Therapy for Menopausal Symptoms," *Journal of Epidemiology and Community Health* 41:26-29, 1987.
 39. Hahn, R. G., Nachtigall, R. D., and Davies, T. C., "Compliance Difficulties with Progestin-Supplemented Estrogen Replacement Therapy," *Journal of Family Practice* 18(3): 411-414, 1984.
 40. Hazzard, W., "Estrogen Replacement and Cardiovascular Disease: Serum Lipids and Blood Pressure Effects," *American Journal of Obstetrics and Gynecology* 161 (6): 1847-1853, 1989.

41. Hemminki, E., Kennedy, D. L., Baum, C., et al., "Prescribing of Noncontraceptive Estrogens and Progestins in the United States, 1974-86," *American Journal of Public Health* 78(11): 1479-1481, 1988.
- 41a. Jenkins, D., Product Manager, Metra Biosystems, Mountainview, CA, personal communication, April, 1995.
42. Jick, S., Walker, A., and Jick, H., "Estrogens, Progesterone, and Endometrial Cancer," *Epidemiology* 4(1):20-24, 1993.
43. Johannes, C. B., Crawford, S. L., Posner, J. G., et al., "Longitudinal Patterns and Correlates of Hormone Replacement Therapy Use in Middle-Aged Women," *American Journal of Epidemiology* 140(5):439-452, 1994.
44. Lauritzen, C., "Clinical Use of Oestrogens and Progestogens," *Maturitas* 12(3): 199-214, 1990.
45. Limouzin-Lamothe, M. A., Mairon, N., Joyce, C. R., et al., "Quality of Life After the Menopause: Influence of Hormonal Replacement Therapy," *American Journal of Obstetrics and Gynecology* 170(2):618-624, 1994.
46. Lindsay, R., Hart, D., and Clark, D., "The Minimum Effective Dose of Estrogen for Prevention of Postmenopausal Bone Loss," *Obstetrics & Gynecology* 63(6):759-763, 1984.
47. Lindsay, R., Hart, D., Forrest, C., et al., "Prevention of Spinal Osteoporosis in Oophorectomized Women," *Lancet* 1151-1154, 1980.
48. MacLennan, A. H., MacLennan, A., Wenzel, S., et al., "Continuous Low-Dose Oestrogen and Progestogen Hormone Replacement Therapy: A Randomised Trial," *Medical Journal of Australia* 159(2):102-106, 1993.
49. Magos, A., Brewster, E., Singh, R., et al., "The Effects of Norethisterone in Postmenopausal Women on Oestrogen Replacement Therapy: A Model for Premenstrual Syndrome," *British Journal of Obstetrics and Gynecology* 93: 1290-1296, 1986.
50. Marwick, C., "Hormone Combination Treats Women's Bone Loss," *Journal of the American Medical Association* 272(19):1487, 1994.
51. Maschak, C. A., et al., "The Relation of Physiological Changes to Subjective Symptoms in Postmenopausal Women With and Without Hot Flashes," *Maturitas* 6:301-308, 1985.
52. McKinlay, S. M., and Jeffries, M., "The Menopause Syndrome," *British Journal of Social and Preventive Medicine* 28: 108-115, 1974.
53. Mishell, D., Moore, D., Roy, S., et al., "Clinical Performance and Endocrine Profiles with Contraceptive Vaginal Rings Containing a Combination of Estradiol and D-norgestrel," *American Journal of Obstetrics and Gynecology* 53:277-281, 1978.
54. Murkies, A. L., "Common Problems with Hormone Replacement Therapy," *Australian Family Physician* 21(3):217-218, 1992.
55. Nachtigall, L. E., "Enhancing Patient Compliance with Hormone Replacement Therapy at Menopause," *Obstetrics & Gynecology* 74(4 Suppl.):77S-80S; discussion 81S-83S, 1990.
56. Nathorst-Boos, J., von Schultz, B., and Carlstrom, K., "Elective Ovarian Removal and Estrogen Replacement Therapy—Effects on Sexual Life, Psychological Well-Being and Androgen Status," *Journal of Psychosomatic Obstetrics and Gynecology* 14(4):283-293, 1993.
57. Notelovitz, M., "Hormonal Therapy in Climacteric Women: Compliance and Its Socioeconomic Impact," *Public Health Report* 104(Suppl.):70-75, 1989.
58. Padwick, M. L., Endacott, M. B., and Whitehead, M. I., "Efficacy, Acceptability, and Metabolic Effects of Transdermal Estradiol in the Management of Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 152: 1085-1091, 1985.
59. Padwick, M., Pryse-Davies, J., and Whitehead, M., "A Simple Method for Determining the Optimal Dose of Progestin in Postmenopausal Women Receiving Estrogens," *New England Journal of Medicine* 315:930-934, 1986.

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60. Payer, L., "Do Hormones Have a Direct Effect on Mood?" *A Portrait of the Menopause*, H. Burger and M. Boulet (eds.) (Pearl River, NY: The Parthenon Publishing Group, 1991).
61. *Physicians' Desk Reference*, 49th Ed. (Montvale, NJ: Medical Economics Data Production Company, 1995).
62. Public Health Service, Office of Inspector General, Office of Evaluation and Inspections, *Medication Regimens: Causes of Non-compliance*, OE1-04-89-89121 (Washington, DC: March 1990).
63. Riggs, L., Hermann, H., and Yen, S., "Absorption of Estrogens from Vaginal Creams," *New England Journal of Medicine* 298:195-197, 1978.
64. Ross, R. K., Paganini-Hill, A., Roy, S., et al., "Past and Present Preferred Prescribing Practices of Hormone Replacement Therapy Among Los Angeles Gynecologists: Possible Implication for Public Health," *American Journal of Public Health* 78:516-519, 1988.
65. Rubin, S. M., and Cummings, S.R., "Results of Bone Densitometry Affect Women's Decisions About Taking Measures to Prevent Fractures," *Annals of Internal Medicine* 116(12 pt 1):990-995, 1992.
66. Rud, T., "The Effect of Estrogens and Gestagens on the Urethral Pressure Profile in Urinary Continent and Stress Incontinent Women," *Acta Obstetric et Gynecological Scandinavia* 59:265-270, 1980.
67. Ryan, P. J., Harrison, R., Blake, G. M., et al., "Compliance with Hormone Replacement Therapy (HRT) After Screening for Post Menopausal Osteoporosis," *British Journal of Obstetrics and Gynecology* 99:325-328, 1992.
68. Sitruk-Ware, R., "Estrogen Therapy During Menopause: Practical Treatment Recommendations," *Drugs* 39(2):203-217, 1990.
69. Speroff, T., Dawson, N., Speroff, L., et al., "A Risk-Benefit Analysis of Elective Bilateral Oophorectomy: Effect on Changes in Compliance with Estrogen Therapy on Outcome," *American Journal of Obstetrics and Gynecology* 164(1 Pt 1): 165-174, 1991.
70. Sporrang, T., Hellgren, M., Samsioe, G., et al., "Comparison of Four Continuously Administered Progestogen Plus Estradiol Combinations for Climacteric Complaints," *British Journal of Obstetrics and Gynecology* 95:1042-1048, 1988.
71. Stevenson, J. C., "Strategies to Increase Estrogen Acceptance and Utilization and to Decrease Side Effects," *Postgraduate Medicine Spec. No.:*15-17; discussion 33-43, April 1989.
72. Stevenson, J., Cust, M., and Gangar, K., "Effects of Transdermal Versus Oral Hormone Replacement Therapy on Bone Density in Spine and Proximal Femur in Postmenopausal Women," *Lancet* 336:265-269, 1990.
73. Studd, J., Thorn, M., Paterson, M., et al., "The Prevention and Treatment of Endometrial Pathology in Postmenopausal Women Receiving Estrogen," *The Menopause and Postmenopause*, N. Pasetto, R. Paoletti, and J.L. Ambrus (eds.) (Lancaster, England: MTP Press, 1980.)
74. Stumpf, P. G., and Trolice, M. P., "Compliance Problems with Hormone Replacement Therapy," *Obstetrics and Gynecologic Clinics of North America* 21(2):219-229, 1994.
75. Tatarzyn, I. V., Lomax, P., Meldrum, D. R., et al., "Objective Techniques for the Assessment of Hot Flashes," *Obstetrics & Gynecology* 57:340, 1981.
76. Thorn, M., Collins, W., and Studd, J., "Hormonal Profiles in Post-Menopausal Women After Therapy with Subcutaneous Implants," *British Journal of Obstetrics and Gynecology* 88:426-433, 1981.
77. Thompson, B., Hunt, S. A., Pumo, D., "Menopausal Age and Symptomatology in General Practice," *Journal of Biological Science* 5:71-82, 1973.
78. Transdermal HRT Investigators Group, "A Randomized Study to Compare the Effective-

- ness, Tolerability, and Acceptability of Two Different Transdermal Estradiol Replacement Therapies," *International Journal of Fertility and Menopausal Studies* 38(1):5-11, 1993.
79. Utian, W., "Transdermal Estradiol Overall Safety Profile," *American Journal of Obstetrics and Gynecology* 156: 1335-1338, 1987.
 80. Utian, W. H., "Biosynthesis and Physiologic Effects of Estrogen and Pathophysiologic Effects on Estrogen Deficiency: A Review," *American Journal of Obstetrics and Gynecology* 161: 1828-1831, 1989.
 81. Varner, R. E., "Acute Indication for Hormonal Therapy in the Menopause," *Emergency Medicine* :93-100, Oct. 30, 1990.
 82. Walsh, B., and Shiff, I., "Vasomotor Flushes," *Annals of the New York Academy of Science* 592:346-356, 1990.
 83. Walsh America/PDS, *PDS Beta Premarin Patient Study*, Wyeth-Ayerst, 0690-9001-4060 (Phoenix, AZ: January 1991).
 84. Weinstein, L., Bewtra, C., and Gallagher, J., "Evaluation of a Continuous Combined Low-Dose Regimen of Estrogen-Progestin for Treatment of the Menopausal Patient," *American Journal of Obstetrics and Gynecology* 162:1534-1539, 1990.
 85. Wentz, W., "Progestin Therapy in Endometrial Hyperplasia," *Gynecologic Oncology* 2:362-367, 1974.
 86. "WHI Trial Discontinues Use of Unopposed Estrogen for Study Participants Due to NHLBI PEPI Findings," *The Blue Sheet* Jan. 18, 1995, pp. 5-6.
 87. Whitehead, M., Hillard, B., and Crook, D., "The Role and Use of Progestins," *Obstetrics & Gynecology* 75(4) :59S-75S, 1990.
 88. Wiklund, I., Berg, G., Hammar, M., et al., "Long-Term Effect of Transdermal Hormonal Therapy on Aspects of Quality of Life in Postmenopausal Women," *Maturitas* 14(3):225-236, 1992.
 89. Wiklund, I., Karlberg, J., and Mattson, L. A., "Quality of Life of Postmenopausal Women on a Regimen of Transdermal Estradiol Therapy: A Double-Blind Placebo-Controlled Study," *American Journal of Obstetrics and Gynecology* 168(3 Pt 1):824-830, 1993.
 90. Williams, D. B., Voigt, B.J., Fu, Y. S., et al., "Assessment of Less than Monthly Progestin Therapy in Postmenopausal Women Given Estrogen Replacement," *Obstetrics & Gynecology* 84(5):787-793, 1994.
 91. Writing Group for the PEPI Trial, "Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factor in Postmenopausal Women," *Journal of the American Medical Association* 273(3):199-208, 1995.