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Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration

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The US Food and Drug Administration (FDA) approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 for treatment of menopausal symptoms. Estrogen sales doubled and tripled in the mid-1960s to mid-1970s, until 1975, when reports of increased endometrial cancer in estrogen users resulted in a dramatic decline. Estrogen use increased again, with evidence of protective effects of progestins on estrogen-induced endometrial changes, combined with a 1982 report that Premarin (conjugated estrogen tablets; Wyeth Pharmaceuticals, Philadelphia, PA) retained bone mass and a 1984 National Institutes of Health (NIH) Consensus Conference on Osteoporosis statement that estrogens were the most effective means for preventing bone loss. Despite conflicting reports in 1985 regarding the relation between estrogens and coronary heart disease (CHD), many published observations of reduced CHD risk in estrogen users—reinforced by clinical trial findings in 1995 of favorable lipoprotein changes in women assigned to CEE with or without a progestin—promoted increased use through the 1990s. By 2001, approximately 15 million US women were using estrogen therapy, with or without progestins. The 2002 Women's Health Initiative (WHI) report of greater harm than benefit of combined CEE plus a progestin resulted in a precipitous decrease in estrogen and progestin use and a serious reevaluation of menopausal hormone therapy, as well as increased interest in alternative approaches to managing menopausal symptoms, including use of "bioidentical" hormones. FDA guidelines regarding treatment indications for vasomotor symptoms, vaginal atrophy, and osteoporosis prevention have resulted in approval of several estrogen (and progestin) formulations, doses, and routes of administration, thereby providing many options for women who seek conventional therapy.

A 1992 background paper from the Office of Technology Assessment (OTA) on menopause, hormone therapy (HT), and women's health, requested by the 102nd US Congress, highlighted the need to conduct randomized clinical trials to assess the short- and long-term health effects of menopausal estrogen and progestin therapy as well as the need for research on alternatives to HT for managing menopausal symptoms.[1] The report recognized the need to understand the natural history of menopause, a universal event in the lives of women, pointing out that in 1991 alone, 1.3 million US women had turned 50 years old, thereby approaching the average age of menopause, and that 35 million US women were already menopausal. (Worth noting is that the first of the baby boomers reached age 45 years in 1990.)

The opinions offered at the National Institutes of Health (NIH) State-of-the-Science Conference on Management of Menopause-Related Symptoms and published herein are not necessarily those of the National Institute on Aging (NIA) and the Office of Medical Applications of Research (OMAR) or any of the cosponsoring institutes, offices, or centers of the NIH. Although the NIA and OMAR organized this meeting, this article is not intended as a statement of Federal guidelines or policy.

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The OTA report acknowledged an absence of good data on the prevalence of HT use and noted considerable geographic variation. Recent evidence suggests that approximately 6 million women were using prescription estrogens in 1992. This number climbed steadily to 15 million over the next decade, largely due to the introduction of a combined estrogen and progestin pill that attracted patients who had not previously received HT, yielding an estimated 6 million women using combined oral HT by 2001.[2]

A decade after publication of the OTA report, the Women's Health Initiative (WHI) trial of combined estrogen and progestin (i.e., the WHI E + P Trial) in 16,608 postmenopausal women with a uterus, aged 50 to 79 years at baseline, was stopped 3 years early, after an average of 5.2 years, because, compared with placebo, the risks (coronary heart disease [CHD], stroke, pulmonary emboli, and breast cancer) had been shown to exceed the benefits (e.g., prevention of hip fracture) in the women assigned to conjugated equine estrogens (CEE) 0.625 mg/day plus daily medroxyprogesterone (MPA) 2.5 mg/day.[3] (CEE and MPA were the most widely prescribed US estrogen and progestin formulations and doses throughout the trial.[2]) A year and a half later, the WHI trial of CEE only (i.e., the WHI E-Alone Trial), involving 10,739 women, posthysterectomy, aged 50 to 79 years, also was stopped early. The primary reason for the trial's termination was an increased incidence of stroke in women assigned to CEE compared with placebo, with no evidence of benefit on CHD risk or overall health.[4]

While the WHI hormone trials were under way, the Study of Women's Health Across the Nation (SWAN), funded by the US National Institute on Aging, the National Institute of Nursing, and the Office of Research on Women's Health, was collecting information on the natural history of menopause in a multiethnic, community-based cohort consisting of thousands of US women aged 42 to 52 years at the outset of a projected 10-year study period. In 2005, the National Institutes of Health (NIH) convened the State-of-the-Science Conference on Management of Menopause-Related Symptoms to achieve consensus on issues for which the WHI trials, SWAN, and several smaller studies could now provide answers to questions raised in the 1992 OTA report to Congress.

This article provides background information regarding estrogens and progestins, including historical context, current US Food and Drug Administration (FDA)–approved formulations, routes of administration and doses, and trends in use, as well as FDA guidance regarding approval for indications of relevance to menopause and a brief description of "natural" or "bioidentical" HT, to help address the following question: What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms?

History and trends in estrogen and progestin use

Estrogens for managing menopausal symptoms

Before the 20th century, the medical profession regarded menopause as a physiologic crisis that could result, under certain circumstances, in disease.[5] It is not clear whether earlier medical concerns focused primarily on the most common menopausal symptoms reported by women today, i.e., vasomotor hot flashes, night sweats, and urogenital symptoms, or on other problems attributed to the "change of life," for which little evidence was available. As early as 1899 the *Merck Manual* featured several treatments for the "climacterica," including a coarse brownish powder available in pills flavored with vanilla or in tablet form, called Ovarin (Ben Labs Ltd., Gujaret, India), which was derived from dried and pulverized cow ovaries and recommended at a dose of 8 to 24 grains 3 times daily.[6,7] Ovarin remained on the market until 1932, about which time oral menopause products, derived from human pregnancy urine, were developed by Adolph Butenandt of Schering AG (Berlin, Germany) and James Bertram Collip of Ayerst (Montreal, Quebec, Canada), to be replaced in the late 1930s by products from the urine of pregnant mares, including the Canadian product Premarin (CEE tablets; Wyeth-Ayerst, Ayerst Organics Ltd., Markham, Ontario, Canada).[6,8,9]

As presented in **Table 1**, other routes of administration and formulations of sex hormones had already been introduced, including the self-injections of an extract of testicles of dogs and guinea pigs reported in 1889 by the French physiologist Charles Edouard Brown-Sequard,[10] an estrogen patch for menopausal symptoms, introduced by Searle (Chicago, IL) in 1928,[11] and ethinyl estradiol, patented by Schering in 1937.[8,12] The 1938 publication of the formula for diethylstilbestrol (DES) by London biochemist Charles Dodds prompted several pharmaceutical companies to seek FDA approval to market DES for treatment of menopausal symptoms, which was granted in September 1941.[6] In May 1942, the FDA granted permission to Wyeth-Ayerst (Philadelphia, PA) to market Premarin 1.25 mg for treatment of menopausal symptoms and related conditions.[13] The drug, which was already being prescribed to thousands of Canadian women, was known at the time to contain estrone and equilin and additional estrogens in smaller amounts. The following year, Dr. Robert Greenblatt, an early innovator in hormone delivery systems, and his colleagues published articles on the benefits of testosterone pellets placed under the skin in menopausal women, including the return of "coital pleasure."[8,14,15] By the 1947 publication of the first edition of the *Physician's Desk Reference*, 53 formulations, sold by 23 companies, were listed for treating "menopausal disorders." Several books, written for the general public from the late 1940s and over the course of the ensuing decades, suggested a range of effects of estrogen therapy (ET), thereby promoting its steady increase in use during the

Table 1 Selected historic milestones in menopausal hormone therapy

Year	Description
1889	Brown-Sequard self-administers dog testicular extract to reverse aging
1890s	Ovarin, derived from cow ovaries, used for treating menopause
1928	Estrogen patch for menopausal symptoms, introduced by Searle*
1930s (early)	Oral products derived from human pregnancy urine used for symptoms
1930s (late)	Oral products derived from pregnant horse urine used for symptoms
1937	Ethinyl estradiol patented
1938	Formula for DES published by Dodds
1941	FDA approves marketing of DES for treating menopausal symptoms; Albright suggests DES may stimulate bone formation
1942	FDA approves Premarin† 1.25 mg for treating menopause
1943	Testosterone pellets implanted under the skin reported to improve coital pleasure
1960s	Oral contraceptives introduced to regulate menses, prevent pregnancy
1972	FDA: estrogens "probably effective" for select cases of osteoporosis (DESI)
1970s	Coronary Drug Project randomized trial in men with CHD: CEE (5.0 and 2.5 mg/day) arms stopped due to early excess clotting and cardiovascular disease; risks of blood clot and stroke reported in young women taking (high-dose) oral contraceptives
1975	Increased endometrial cancer risk reported in estrogen users; FDA orders labeling changes to state high risk
1978	FDA mandate: by April, all estrogen products should contain warning with messages that estrogen has been proved effective only for hot flashes and vaginal dryness and carries risks of cancer and blood clot
1985	Conflicting reports published regarding cardiovascular risk in estrogen users: Framingham Heart Study reports increased stroke, blood clot, and coronary risk; Nurses' Health Study reports reduced CHD risk
1986	FDA deems estrogens "effective" therapy for osteoporosis
1990	FDA does not approve estrogen indication for heart disease prevention
1994	FDA Osteoporosis Guidance: prevention requires 2-yr BMD placebo-controlled, randomized trial regardless of baseline BMD; treatment requires fracture reduction in women with osteoporosis at baseline
1995	PEPI trial suggests reduced CHD risk for CEE with or without 1 of 3 progestin arms; first combination estrogen + progestin pill (Prempro‡) is introduced
1998	HERS trial of women with CHD (with intact uterus) reports no CHD benefit of CEE + MPA over 4.1 yr of follow-up; excess risk in first year
2002	WHI E + P trial reports risks of CEE + MPA outweigh benefits over 5.2 yr
2003	FDA "black-box" warning on estrogen products: estrogens and progestins should not be used for prevention of cardiovascular disease; recommends lowest effective dose for shortest duration. FDA assesses but does not approve indication for osteoporosis treatment for combined estrogen + progestin
2004	WHI E-alone trial reports no overall benefit of CEE only over 6.8 yr

BMD = bone mineral density; CEE = conjugated equine estrogens; CHD = coronary heart disease; DES = diethylstilbestrol; DESI = Drug Efficacy Study Implementation; FDA = US Food and Drug Administration; HERS = Heart and Estrogen/progestin Replacement Study; MPA = medroxyprogesterone acetate; PEPI = Postmenopausal Estrogen-Progestin Interventions; WHI = Women's Health Initiative.

*Searle, Chicago, IL.

†Premarin (conjugated equine estrogen tablets; Wyeth Pharmaceuticals, Philadelphia, PA).

‡Prempro (CEE = MPA; Wyeth Pharmaceuticals).

1950s, which doubled and tripled in the mid 1960s to mid 1970s.

Of note, drugs approved before 1962 were required to demonstrate safety but not effectiveness at the time of approval, whereas new drugs were required to demonstrate effectiveness. In 1972, the FDA published a *Federal Register* notice announcing that a number of estrogen products, including Premarin, had been shown to be effective in the treatment of menopausal symptoms based on an evaluation done under the Drug Efficacy Study Implementation (DESI) program designed to assess the effectiveness of drugs approved for marketing before 1962.[13] In the same notice, the FDA provided for submission and approval of abbreviated new drug applications (ANDAs) for generic conjugated estrogens.

The increase in estrogen use continued despite reports in the 1960s and 1970s of increased thrombosis and severe hypertensive episodes in young women who initiated (high-dose, high-potency) oral contraceptives[16] and of increased thromboembolic events and myocardial infarction in men with known heart disease assigned to Premarin (5 mg and 2.5 mg) as participants in the randomized, placebo-controlled Coronary Drug Project.[17,18]

On the other hand, reports in 1975 of increased endometrial carcinoma in users of menopausal ET[19,20] resulted in a precipitous decrease in estrogen use. Following these reports, the FDA ordered labeling changes of estrogen products to state the potentially lethal effect and high risk; according to an FDA mandate, all estrogen products and birth control pills were supposed to contain a comprehensive warning by April 1978, to be dispensed by the pharmacist at the point of sale, to inform users that estrogen had been proved effective only for hot flashes and vaginal dryness but carried risks of cancer and blood clots.[6,8] Subse-

quent evidence that the addition of a progestin could prevent estrogen-induced endometrial changes halted the pattern of decline, and estrogen use increased steadily from the early 1980s through the 1990s, accompanied by an increase in progestin use by women with a uterus. During this period, when women were being educated about osteoporosis and the fact that heart disease was the leading cause of death in women, the steep increase in menopausal hormone use was likely attributable to the publication of numerous reports suggesting that ET prevents bone loss attributed to menopause and revealing epidemiologic evidence of lower CHD incidence in estrogen users.

In 1990, the FDA published a proposal to withdraw from the market generic forms of conjugated estrogen tablets owing to the potential for bioinequivalence and consequent concerns about safety and efficacy. This proposal, which was endorsed by the FDA's Generic Drugs Advisory Committee in 1991, resulted in FDA withdrawal of approval of all ANDAs.[13] ANDAs for conjugated estrogen tablets were submitted in 1994, after a 1970 US Pharmacopeia (USP) monograph describing conjugated estrogens as containing sodium estrone sulfate and sodium equilin sulfate was amended in 1992 to include 3 additional estrogens, and in 1995 after Wyeth-Ayerst filed a citizen petition requesting the FDA designate δ-dehydroestrone sulfate (DHES) a concomitant component of conjugated estrogens.[8,9] In May 1997, the FDA's Center for Drug Evaluation and Research (CDER) announced that it would not approve synthetic generic forms of Premarin because they had not been shown to have the same active ingredients as the original drug for treating menopausal symptoms and preventing osteoporosis.[13]

Estrogens for preventing osteoporosis

A link between low ovarian hormone levels and increased bone loss was reported in 1941 by Albright and colleagues,[21] who proposed that DES may be a stimulus for bone formation. Three decades later, the 1972 FDA *Federal Register* notice on estrogen products, including Premarin, announced that they were "probably effective" for prevention of osteoporosis.[13] A decade after that, Genant and coworkers[22] reported that in women undergoing surgical menopause, intermediate doses of Premarin maintained bone mass better than low doses of Premarin or placebo, and evidence presented at a 1984 NIH Consensus Development Conference on Osteoporosis resulted in a conclusion that estrogens were the most effective means to prevent bone loss.[23] In 1986, the FDA announced in the *Federal Register* that short-acting estrogens, including Premarin, were found to be effective for preventing osteoporosis.[13]

The FDA Osteoporosis Guidance was updated in 1994 to distinguish between prevention—based on benefits to bone mineral density (BMD)—and treatment, based on fracture reduction in subjects with osteoporosis at baseline. Although Premarin was already approved for prevention, the 3-year, randomized, placebo-controlled Postmenopausal Estrogen-Progestin Interventions (PEPI) trial confirmed the indication of prevention with a clear demonstration of benefit in both lumbar and hip BMD with CEE alone or combined with any of 3 progestin regimens, including both daily and cyclic MPA and cyclic micronized progesterone, compared with placebo.[24]

Estrogens for preventing heart disease

In 1985, the Framingham Heart Study reported a nearly 2-fold increase in risk for cardiovascular disease (CVD) associated with estrogen use over an 8-year period for 1,234 postmenopausal women aged ≥50 years.[25] This observation appeared back-to-back with the first Nurses' Health Study report of 50% lower risk of CHD in ever- versus never-users of estrogen, for an average 3.5 years of follow-up of 32,317 postmenopausal women aged 30 to 55 years.[26] The discrepancy between the results of these 2 highly respected prospective cohort studies was attributed to inclusion in the Framingham study of cardiovascular events other than MI and CHD (e.g., angina pectoris, intermittent claudication, transient ischemic attack) and adjustment for high-density lipoprotein (HDL) cholesterol, which was considered possibly inappropriate because, at the time, it was thought to be the most plausible mechanism of action for estrogen. Within the next few years, several other cohort studies corroborated the Nurses' Health Study finding of reduced CHD risk, including the Lipid Research Clinics Follow-up Study of 2,270 women aged 40 to 69 years who were followed for 8.5 years,[27] the Leisure World Study of 8,841 women aged 40 through 101 years who were followed for 5.5 years,[28] and a Kaiser Permanente program cohort of 6,093 women aged 18 to 54 years who were followed for 10 to 13 years.[29] In a 1991 review, Barrett-Connor and Bush[30] acknowledged that the weight of the evidence pointed toward a substantial reduction in CHD risk among women using estrogens; however, they also pointed out that overall, women who took estrogen after the menopause were more likely to be white, educated, upper-middle class, and lean, and thereby at lower risk of heart disease than women who did not use ET.

In 1991, an FDA Advisory Committee voted almost unanimously in favor of an industry request for an indication for ET for reducing the risk of CHD in postmenopausal women; however, this recommendation was never acted on by the FDA.[11] In 1992, the American College of Physicians published a position statement proposing that all postmenopausal women should be offered HT to help prevent heart disease.[31] The recommendation followed a landmark meta-analysis of observational studies by Grady and associates,[32] which reported that postmenopausal hormone use was associated with approximately 33% less fatal heart disease compared with nonuse and suggested that because of the greater prevalence of heart disease, this benefit would prevent more deaths than would be caused by the combined increased risk of death due to breast and uterine cancers.[32] Other prominent professional organizations soon followed with similar recommendations.[11]

The 1995 PEPI clinical trial findings of favorable lipoprotein changes in women assigned to CEE with or without a progestin reinforced the belief that estrogens reduce CHD risk but also showed that the addition of cyclic or daily MPA reduced the beneficial effect of estrogen on HDL cholesterol.[33] Although substantially fewer data were available for combined estrogen plus progestin than for estrogen monotherapy, meta-analyses based on all published observational studies through mid 1997 revealed a summary estimate of the relative risk (RR) for CHD of 0.70 for women who ever used unopposed estrogen compared with never-users (95% confidence interval [CI], 0.65–0.75), with CEE being the predominant regimen. A similar risk estimate was observed in the 7 studies of women who reported treatment with estrogen plus a progestin, usually cyclic MPA, relative to never-users (RR, 0.66; 95% CI, 0.53–0.84).[34] Among the CEE-only studies, 3 angiographic studies of women with CHD showed reduced CHD risk, whereas there were no such studies for combination therapy.[34]

The first large clinical trial specifically designed to evaluate HT for CHD was the Wyeth-funded Heart and Estrogen/progestin Replacement Study (HERS), which randomly assigned 2,763 postmenopausal women (mean age, 67 years) with documented CHD to daily CEE 0.625 mg plus MPA 2.5 mg or placebo for an average of 4.1 years.[35] The HERS trial found no overall difference in the primary outcome (nonfatal MI and CHD death), despite significant lowering of low-density lipoprotein cholesterol and an increase in HDL cholesterol. However, in the first year, there was a statistically significant excess risk of CHD events in the CEE plus MPA group (hazard ratio [HR], 1.52; 95% CI 1.01–2.29).[35] Within the next few years, several smaller secondary prevention trials also reported no benefit after HT, including estrogens other than CEE and regimens without a progestin, and some suggested harm.[11] It was proposed that for women who already had coronary atherosclerosis, it was too late for ET, thereby increasing interest in the NIH-funded WHI trials that were designed to evaluate primary prevention.

As discussed earlier, the preliminary report of the WHI E + P trial, published at the time the trial was stopped, showed a significant increase in CHD outcomes.[3] Final analyses, which included additional cases and were based on centrally adjudicated outcomes over an average of 5.6 years of follow-up, revealed an HR for CHD of 1.24 (95% CI, 1.00–1.54), thereby just failing to reach significance; however, the elevation in risk was most apparent, and significant, in the first year (HR, 1.81; 95% CI, 1.09–3.01),[36] consistent with both the CEE effects seen in the men with CHD in the Coronary Drug Project[17,18] and the CEE plus MPA effects observed in women with CHD in the HERS trial.[35]

Whereas, the percent of US women aged 50 to 74 years exposed to HT had reached an estimated 33% in 1995 and climbed to 42% by 2001, there was a precipitous decline in use immediately following the publication of the preliminary findings of the WHI E + P trial, with Prempro (CEE-MPA; Wyeth Pharmaceuticals) prescriptions dropping by 66% and Premarin prescriptions dropping by 33% between January to June 2002 and January to June 2003.[2] Use of other oral estrogens decreased by 23%, use of transdermal estrogens declined by 14%, and use of other oral combination estrogen/progestins dropped by 19%, whereas vaginal estrogen use increased by 7% during this period.[2] If prescription rates observed through July 2003 remain stable, rates similar to 1995 are projected for 2005.

Follow-up of a randomly selected group of 377 members of the Kaiser Foundation Health Plan aged 50 to 69 years, who had used HT regularly for ≥1 year before July 2002 and who had attempted to stop between July 2002 and March 2003, revealed that the vast majority (74%) successfully stopped. Most successful stoppers (71%) quit HT abruptly, whereas 29% tapered off therapy; there was no difference in the incidence of troublesome withdrawal symptoms or successful quitting between these groups. For the 26% of women who resumed taking HT, the major predictor of resumption was the development of troublesome withdrawal symptoms. Women who had undergone a hysterectomy, who had used HT for ≥10 years, and who started mainly for reasons other than health promotion were more likely to be unsuccessful in quitting.[37]

WHI E + P trial participants who were still taking study pills at the time that trial was stopped, an average of 5.7 years after randomization, were asked to complete a survey mailed 8 to 12 months after the stop date, which 89.9% of eligible participants returned. Moderate or severe vasomotor symptoms were reported by 21.2% of the former CEE + MPA group and 4.8% of placebo group respondents after discontinuing study pills, overall, and by 55.5% and 21.3%, respectively, of participants who had reported these symptoms at baseline.[38] Moderate or severe vasomotor symptoms and pain or stiffness were significantly more likely to occur among respondents who had been in the active hormone group, compared with placebo, and these symptoms were more prevalent in participants who reported the same at baseline.[38] The respondents reported a wide range of strategies to manage these symptoms. It would be interesting to know whether a substantially lower proportion of women would have experienced symptoms if they had taken a lower dose of CEE, or a different estrogen, over this period.

US Food and Drug Administration–approved estrogens and progestins

At the time of this writing, various formulations of estrogens (**Table 2**), progestins (**Table 3**), and estrogen-progestin (and estrogen-testosterone) combinations (**Table 4**) were approved for treating vasomotor and/or vulvar and vaginal atrophy associated with the menopause. As shown in Table 2, routes of estrogen administration include oral (pill), transdermal (patch), creams, gels, topical emulsions, and a vaginal ring; several oral and transdermal formula-

Table 2 US Food and Drug Administration (FDA)–approved estrogens with an indication for both vasomotor symptoms and vaginal atrophy (except as noted)

Route of Administration	Formulation	Product Name
Oral (pill)	CEE	Premarin*
	Micronized 17β-estradiol	Estrace[†]
	Synthetic (plant-based) CEE	Cenestin[‡]
	Esterified estrogens	Estratab[§], Menest[‖]
	Estropipate	Ortho-Est[¶], Ogen[#]
Transdermal (skin patches)	Micronized 17β-estradiol	Alora**
		Esclim[¶]
		Estraderm[††]
		Menostar[‡‡]
		Vivelle-Dot[§§]
		Climara[‡‡] (once-a-week)
Creams (topical)	CEE	Premarin
	Micronized 17β-estradiol	Estrace
	Dienestrol	Ortho Dienestrol[‖‖] (only for vaginal atrophy)
Gels	Estradiol gel	EstraGel[¶¶]
Topical emulsion	Estradiol	Estrasorb[##] (not for vaginal atrophy)
Vaginal ring	Micronized 17β-estradiol (brief initial peak in blood levels)	Estring[#] (only for vaginal atrophy)

CEE = conjugated equine estrogens.
*Wyeth Pharmaceuticals, Philadelphia, PA.
[†]Bristol-Myers Squibb, New York, NY.
[‡]Durmaed Pharmaceuticals Inc., Cincinnati, OH.
[§]Solvay Pharmaceuticals, Baudette, MN.
[‖]King Pharmaceuticals, Inc., Bristol, TN.
[¶]Women First HealthCare Inc., San Diego, CA.
[#]Pharmacia & Upjohn, Kalamazoo, MI.
**Watson Pharma Inc., Morristown, NJ.
[††]Novartis Pharmaceuticals Corp., East Hanover, NJ.
[‡‡]Berlex Inc., Montville, NJ.
[§§]Novogyne Pharmaceuticals (Novartis/Novogen), East Hanover, NJ.
[‖‖]Product no longer available. Formerly, Ortho-McNeil Pharmaceutical Inc., Raritan, NJ.
[¶¶]Unimed Pharmaceuticals, Inc., a Solvay Pharmaceuticals company, Marietta, GA.
[##]Novavax, Inc., Columbia, MD.

tions are indicated for treatment of both vasomotor symptoms and symptoms of vulvar and vaginal atrophy. When hormones are prescribed solely for vulvar and vaginal symptoms, topical vaginal products should be considered, per FDA labeling, although it should be noted that significant systemic absorption may occur with the use of vaginal creams, which could potentially result in premenopausal blood levels of estrogens. As shown in Table 3, only MPA and micronized progesterone pills are approved by the FDA for managing estrogen-induced hyperplasia, even though others—which are indicated for contraception and/or regulating menses—are often prescribed with menopausal ET. In contrast, all combination therapies (Table 4) are indicated for treating both vasomotor and vulvar/vaginal symptoms associated with menopause, and the progestins are indicated for managing estrogen-induced hyperplasia.

Table 5 presents the estrogen and estrogen-progestin formulations and doses approved for preventing osteoporosis at the time this article was written. When prescribing solely for the prevention of osteoporosis, therapy should be considered for women at significant risk of osteoporosis only after nonestrogen medications have been carefully considered, per FDA labeling. In addition, the recommended starting dose is the equivalent of 0.3 mg CEE (plus 1.5 mg MPA).

US Food and Drug Administration recommendations for clinical evaluation of estrogen and estrogen-progestin products and prescribing information

The FDA provides Guidance for Industry documents[39,40] for studies of estrogen and estrogen-progestin drug products for the treatment of moderate-to-severe vasomotor symptoms (hot flashes) and treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy associated with the menopause. The severity of vasomotor symptoms is defined as mild, sensation of heat without sweating; moderate, sensation of heat with sweating, able to continue activity; and severe, sensation of heat with sweating causing cessation of activity.

Table 3 US Food and Drug Administration (FDA)–approved progestins with an indication for managing estrogen-induced hyperplasia versus indication only for contraception

Route of Administration	Formulation	Product Name
Oral (pills)*	MPA	Provera, Amen, Cycrin[†]
	Micronized progesterone USP (in peanut oil)	Prometrium[‡]
Oral (pills)[§]	Norethindrone	Micronor[‖], Nor-QD[¶]
	Norethindrone acetate	Aygestin[#]
	Norgestrel	Ovrette**
	Levonorgestrel	Norplant**
Intrauterine devices[§]	Levonorgestrel	Mirena[††]
	Progesterone	Progestasert[‡‡]
Vaginal gel[§]	Progesterone	Crinone**

MPA = medroxyprogesderone acetate; USP = US Pharmacopeia.
*Indicated for management of estrogen-induced hyperplasia.
[†]All Pharmacia & Upjohn, Kalamazoo, MI.
[‡]Walter Bushnell Pvt. Ltd., Bombay, Maharastra, India.
[§]Indicated only for contraception.
[‖]Janssen-Cilag, Ltd., London, England.
[¶]Watson Pharma Inc, Morristown, NJ.
[#]Durmaed Pharmaceuticals Inc., Cincinnati, OH.
**Wyeth Ayerst Laboratories, Philadelphia, PA.
[††]Berlex Inc., Montville, NJ.
[‡‡]ALZA Corp., Fridley, MN.

Table 4 US Food and Drug Administration (FDA)–approved estrogen-progestin or estrogen-testosterone combinations with an indication for both vasomotor symptoms and vaginal atrophy

Route of Administration	Formulation	Product Name
Oral (pills)	CEE + daily MPA	Prempro*
	CEE + cyclic MPA	Premphase*
	Ethinyl estradiol + norethindrone acetate	FemHRT[†]
	17β-estradiol + norethindrone	Activella[‡]
	Estradiol + norgestimate	Ortho-Prefest[§]
	Esterifed estrogens + methyltestosterone	Estratest[‖]
Transdermal (skin patches)	17β-estradiol + norethindrone acetate	Combipatch[¶]
	Norgestimate	Ortho-Prefest
Injection	Estradiol + testosterone cypionate	Depo-Testadiol[‡]

CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate.
*Wyeth Pharmaceuticals, Philadelphia, PA.
[†]Parke-Davis, Warner-Lambert/Pfizer, New York, NY.
[‡]Pharmacia & Upjohn, Kalamazoo, MI.
[§]Ortho-McNeil, Inc., Bristol, TN.
[‖]Solvay Pharmaceuticals, Baudette, MN.
[¶]Novartis Pharmaceuticals Corp., East Hanover, NJ.

Patient self-assessed symptoms of vulvar and vaginal atrophy (each rated as none, mild, moderate, or severe) include vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, and vaginal pain associated with sexual activity. Vaginal bleeding associated with sexual activity is assessed as present or absent.

Recommended inclusion and exclusion criteria[39] are that only postmenopausal women be included, with "postmenopausal" defined as either 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with follicle-stimulating hormone >40 mIU/mL (40 IU/L) or 6 weeks postsurgical bilateral oophorectomy. For the indication of treatment of vasomotor symptoms, study participants should have a minimum of 7 or 8 moderate to severe hot flashes per day (or 50 to 60 hot flashes per week) at baseline. For the indication of treatment of vulvar and vaginal atrophy, each participant should (1) have self-identified ≥1 moderate to severe symptom that she considers bothersome; (2) have ≤5% superficial cells on a vaginal smear; (3) and have a vaginal pH >5.0. Participants should not be taking estrogen alone or combined with a progestin. Washout periods range from 1 week for vaginal products (creams, gels, rings) to ≥6 months for pellet therapy or progestin injectable drug therapy. Women >40 years of age should have documentation of a negative screening mammogram

Table 5 US Food and Drug Administration (FDA)–approved estrogens or estrogen-progestin (or estrogen-testosterone) combinations and doses with an indication for osteoporosis prevention

Products (specific hormone)	Doses (mg/day)
Oral estrogens (pills)	
Premarin (CEE)*	2.5, 1.25, 0.90, 0.625, 0.45, 0.30
Estrace (estradiol)†	2.0, 1.0, 0.5
Ogen (estropipate)‡	0.75
Ortho-Est (estropipate)§	0.75
Transdermal estrogens (patch)	
Vivelle (estradiol)‖	0.025–0.10
Climara (estradiol)¶	0.025–0.10
Oral estrogen combinations (pills)	
Prempro (CEE/MPA)*	0.625/5.0, 0.625/2.5, 0.45/1.5, 0.30/1.5
Ortho-Prefest (estradiol/norgestimate)#	1.0/0.9
Activella (estradiol/norethindrone)‡	1.0/0.5
FemHRT (ethinyl estradiol/norethindrone)**	0.5/1.0

CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate.
*Wyeth Pharmaceuticals, Philadelphia, PA.
†Bristol Myers Squibb, New York, NY.
‡Pharmacia & Upjohn, Kalamazoo, MI.
§Women's First Healthcare Inc., San Diego, CA.
‖Novogyne Pharmaceuticals (Novartis/Novogen), East Hanover, NJ.
¶Berlex Inc., Montville, NJ.
#Ortho-McNeil, Bristol, TN.
**Parke-Davis, Warner-Lambert/Pfizer, New York, NY.

and normal clinical breast examination. All subjects who have an intact uterus should have an endometrial biopsy performed at screening to exclude those with endometrial hyperplasia or cancer.

Labeling for healthcare providers

Labeling for healthcare providers[40] includes "black-box" warnings as given below.

Estrogens increase the risk of endometrial cancer

The need for close clinical surveillance and adequate diagnostic monitoring, including endometrial sampling, is stressed. It should also be stated that there is no evidence that "natural" estrogens result in a different endometrial risk profile than do synthetic estrogens at equivalent doses.

Cardiovascular and other risks

Estrogens with or without progestins should not be used for the prevention of CVD or dementia. This statement is followed by brief reports of the results of the WHI E-Alone[4] and WHI E + P[3] trials and the Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, which reported increased risk of developing probable dementia in postmenopausal women aged ⩾65 years during 5.2 years of treatment with CEE 0.625 mg alone[41] and during 4 years of treatment with CEE 0.625 mg combined with MPA 2.5 mg,[42] relative to placebo. (It is stated that it is unknown whether this finding applies to younger postmenopausal women.)

Labeling for patients

Labeling for patients[40] includes "black-box" warnings that estrogens increase the risk for developing cancer of the uterus, with instructions to report any vaginal bleeding, and the instructions: "Do not use estrogens with or without progestins to prevent dementia." These instructions are followed by the statements: "Using estrogens with or without progestins may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots" and "Using estrogens with or without progestins may increase your risk of dementia."

Osteoporosis

As mentioned previously, in 1994 the FDA updated its Osteoporosis Guidance to distinguish between prevention and treatment. To approve an indication for the prevention of osteoporosis, estrogens and estrogen-progestin combinations had to have been designated DESI drugs or to demonstrate maintenance of lumbar spine BMD in a 2-year, randomized, placebo-controlled trial in subjects without osteoporosis at baseline, with a sample size generally <500. In contrast, an indication for treatment requires reduction in the incidence of fracture in a 3-year, randomized, controlled trial in women with osteoporosis at baseline. Following publication of the reduced hip and other fracture in the WHI E + P trial[3,43] the FDA reviewed the evidence to support an

indication of treatment of osteoporosis for estrogen-progestin combinations but decided against this, noting that subjects participating in WHI generally did not have osteoporosis at baseline. The evidence of health risks exceeding benefits in the overall trial also was noted, as was the fact that even for women at high risk for fracture, the global index suggested no overall benefit of CEE plus MPA.[43] Currently, no estrogen (or progestin) product has an FDA indication for treatment of osteoporosis.

Bioidentical hormones

Safety concerns following the report of the WHI E + P trial are likely to reflect increased interest in "natural" or "bioidentical" HT (i.e., treatment with individually compounded formulations of certain steroids in various dosage forms, including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol) in a compounded dosage form based on individual salivary hormone concentrations.[44] There is, however, concern that salivary testing is not a reliable means to determine precise hormone levels.

Examples of individually prepared natural estrogens[44] include biestrogen (Biest), which refers to a combination estrogen preparation of 20% estradiol and 80% estriol, expressed on a milligram-per-milligram basis. A similar preparation, triestrogen (Triest) is reported to contain 10% estradiol, 10% estrone, and 80% estriol. These products are not commercially marketed but instead are compounded in pharmacies at the request of the prescribing physician. In fact, estriol is not commercially marketed for oral use in the United States, either as a single entity or in combination with other ingredients.

Proponents claim that bioidentical hormones are better tolerated than manufactured products and are safer alternatives to pharmaceutical dosage forms of estrogens and/or progestogens. However, FDA guidance specifically recommends that labeling include a statement to the contrary, i.e., that there is no evidence that natural products are safer than synthetic products. Unfortunately, there are few observational studies or clinical trials comparing conventional HT with bioidentical HT; therefore, there is little evidence to support an advantage of individualized hormone dosing over conventional therapies and, at present, the use of such therapy is not supported by evidence regarding pharmacokinetics, safety, and efficacy.[44]

Summary

Of interest, FDA approval criteria do not promote research on effectiveness of hormones in women who are in either early or late perimenopause, a large proportion of whom experience moderate to severe menopausal symptoms that often subside before they reach the 12th month after their last menses. Although millions of women are eager to identify the safest and most effective approach to managing menopausal symptoms, head-to-head comparisons of the many available estrogen and progestin formulations and regimens are limited; therefore, a woman's decision largely depends on her preferences with respect to route of administration (i.e., oral versus transdermal or other forms). There also is little comparative information regarding bioidentical versus conventional hormones. Finally, relatively little information exists regarding the best approach to stopping hormones—despite the FDA recommendation to use these products for the "shortest duration" possible—or the optimal dose or route of administration, with respect to risk for experiencing symptoms when stopping menopausal HT.

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