VIEWPOINT

WOMEN'S HEALTH

Updated Labeling for Menopausal Hormone Therapy

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The role of estrogen replacement for perimenopausal and menopausal women has been the subject of controversy. In the mid-20th century, clinicians observed that women who underwent bilateral oophorectomy before menopause faced heightened cardiovascular disease risk, suggesting that estrogen may have cardioprotective effects. In 1942, the US Food and Drug Administration (FDA) approved the first formulation for the treatment of menopausal symptoms.

Current evidence suggests that hormone therapy initiated within a decade of the onset of perimenopause has been associated with numerous long-term health benefits, including reduced vasomotor symptoms, without significantly affecting atherosclerotic cardiovascular disease among younger postmenopausal women aged 50 to 59 years.[1] Hormone therapy has also been associated with a 25% to 50% reduction in fatal cardiovascular events[2] (the leading cause of death in women), a 50% to 60% reduction in bone fractures,[3] a 64% reduction in cognitive decline,[4] and a 35% decreased risk of Alzheimer disease.[5] Currently, there are more than 20 estrogen-alone and combined estrogen-progestogen products in various doses and formulations. With the exception of antibiotics and vaccines, there may be no medication in the modern world that can improve the health outcomes of older women on a population level more than hormone therapy. In addition, hormone therapy is FDA approved to treat moderate to severe menopausal symptoms, such as hot flashes, night sweats that could lead to debilitating sleep disruption, and mood changes. Following the release of findings from the 2002 Women's Health Initiative (WHI), hormone therapy prescriptions decreased due to fears that hormone therapy increased a woman's risk of dying of breast cancer. The increased risk in breast cancer cases observed in the original WHI study (1 additional nonfatal breast cancer diagnosis per 1000 women treated in a year) has been subsequently recognized to be attributed to the particular progesterone formulation used in the study, medroxyprogesterone acetate—a formulation that is not in common use today for hormone therapy. The WHI trials in 2002 (estrogen-progestin trial) and 2004 (estrogen-only trial) evaluated the benefits and risks of 1 type and dose of estrogen and progestin for prevention of cardiovascular disease and other chronic medical conditions in postmenopausal women aged 50 to 79 years. These trials did not require hormone therapy initiation before age 60 years or within 10 years of menopause—when menopausal symptoms are typically most pronounced and a window of opportunity before permanent vascular narrowing and hardening occur. When hormone therapy is given later, the cardiovascular benefits of hormone therapy appear to invert.

Starting in January 2003, in response to the WHI estrogen-progestin trial results and after various public announcements and the October 2002 National Institutes of Health–sponsored public forum, the FDA began instituting class-wide labeling changes for estrogen-alone and combined estrogen-progestogen products approved for menopausal symptoms and osteoporosis. These changes would eventually include the addition of boxed warnings on the serious risks seen in the WHI trials. The box warnings described risks of cardiovascular disease, thromboembolism, breast cancer, and probable dementia without stratifying by age of initiation. Clinicians then only infrequently offered hormone therapy to perimenopausal and postmenopausal women because of the black box warnings. Today, hormone therapy is available in formulations that do not appear to carry the same increased risk of blood clots or breast cancer that was seen in earlier studies. Subsequent analyses and observational studies have highlighted the importance of initiating hormone therapy within 10 years of onset of menopause. Timing of initiation appears to be critical in determining the risk-benefit ratio.[6-8] Compared with the 63-year-old average age in the WHI trials, women who present with new onset of moderate to severe vasomotor symptoms needing treatment tend to be younger (generally younger than 60 years). Data from this cohort of younger women suggest that initiating hormone therapy within 10 years of menopause reduces all-cause mortality in the subsequent decade. This age-dependent differential risk has prompted renewed appraisal to support a more nuanced interpretation of hormone therapy's benefit-risk balance. Furthermore, clinical trials have never found an increased risk of breast cancer mortality from hormone therapy.

Recent developments at the FDA, including the July 2025 Expert Panel and public engagement via Federal Register docket (FDA-2025-N-2589), reflect a growing recognition of the need to revisit hormone therapy labeling. For example, many commenters described debilitating genitourinary symptoms, reported substantial relief with local vaginal estrogen, and requested different labeling than systemic hormones. The FDA also conducted drug utilization analyses to characterize prescribing patterns and the extent of hormone therapy use among menopausal and postmenopausal women.

With a growing awareness of the limitations of the WHI and a refined understanding of various hormone therapy regimens, the FDA is removing the boxed warnings from the following products:

- All combined estrogen-progestogen
- Estrogen alone
- Other estrogen containing
- Progestogen only

FDA label changes aim to clarify risk communication, incorporate emerging evidence, and distinguish between systemic and topical therapies in a manner consistent with the most current understanding of the nuanced benefit-risk balance of hormone therapy.

The evidence basis for the labeling changes included a comprehensive FDA evaluation of WHI and post-WHI publications, with

particular attention to evidence related to timing, duration, and risks associated with hormone therapy use during the earlier postmenopausal years.[6-8] While boxed warnings are changing, all of the underlying adverse event information will continue to appear in the package insert.

The FDA's hormone therapy label updates include

- Removal of boxed warnings (cardiovascular disease, stroke, breast cancer, probable dementia), except for the boxed warning in systemic estrogen labels for endometrial cancer with unopposed estrogen in women with a uterus, as it is important to remind health care practitioners and patients that this serious risk can be mitigated by adding a progestogen.
- Removal of the recommendation to prescribe hormone therapy at the lowest effective dose for the shortest duration—treatment decisions are individualized and fall within the clinical judgment of a clinician in discussion with a patient.
- Tailored safety information: Instead of applying identical class-based language across all hormone therapy labels, safety data will be revised to reflect risks most relevant to each specific type of hormone therapy product (eg, combined estrogen plus progestogen vs estrogen alone).
- For the topical vaginal estrogen-only drug label, the emphasis is on the safety findings most relevant to topical vaginal use and not the broader warnings associated with systemic exposure.
- Timing information for systemic hormone therapy: Labels will include updated guidance on initiating treatment in women younger than 60 years or within 10 years of menopause onset to optimize the benefit-risk balance.

These labeling revisions signal a meaningful shift toward more nuanced, evidence-based communication of hormone therapy risks—one that prioritizes clinical relevance, distinguishes between different formulations and patient populations, and balances the narrative to reflect both safety and therapeutic value. It may also reduce the outsized fear that has prevented approximately 50 million women from the short- and long-term health benefits of this therapy. If implemented, these changes may guide appropriately tailored hormone therapy use and optimize individualized care.

ARTICLE INFORMATION

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