The Food and Drug Administration boxed warning on menopausal hormone therapy: history, impact, and a regulatory inflection point in women's health

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Abstract

The removal of the Food and Drug Administration boxed warning from menopausal hormone therapy (MHT) products in November 2025 marks a historic regulatory inflection point in women's health. This manuscript reviews the history and purpose of boxed warnings, examines the Women's Health Initiative–era rationale that led to the class-wide application of boxed warnings across all MHT formulations and routes of administration, and analyzes the long-term clinical, educational, and public health consequences of MHT avoidance driven largely by this regulatory action. We synthesize decades of post Women's Health Initiative evidence demonstrating substantial heterogeneity in MHT risk and benefit by age, timing of initiation, formulation, and route of administration. To contextualize the lifecycle of the MHT boxed warning, we compare it with three instructive regulatory parallels: canagliflozin, illustrating regulatory agility when benefit- risk balance evolves; varenicline, showing how a boxed warning led to a sharp decline in prescribing that was later not supported by randomized trial evidence; and topical calcineurin inhibitors, highlighting the pitfalls of route-agnostic class-effect labeling. We further examine the persistent impact of the boxed warning on prescribing patterns, menopause education, and primary care training, and propose a framework for regulatory reform and necessary clinician education.

Key Words: FDA boxed warning, Menopausal hormone therapy, Women's Health Initiative.

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The removal of the boxed warning, formerly known as the black box warning, from all menopausal hormone therapy (MHT) products on November 10, 2025, marks a historic inflection point in menopause care.[1] This manuscript reviews the history of boxed warnings, outlines the Women's Health Initiative (WHI)-era rationale and the subsequent class-wide application of MHT boxed warnings across routes of administration, examines the clinical and public health consequences of MHT avoidance largely due to the boxed warning, addresses training gaps in primary care, and proposes future directions to improve both access to menopause treatment and research. Decisively, we provide context for the MHT boxed warning using three medication parallels: canagliflozin, illustrating how boxed warnings can be removed expeditiously when benefit-risk balance evolves; varenicline, demonstrating population-level harms from decreased prescribing due to boxed warnings that were later contradicted and removed by randomized evidence; and topical calcineurin inhibitors (TCIs), highlighting the pitfalls of applying class-effect warnings across formulations with profoundly different systemic exposures.

The Food and Drug Administration (FDA) originally placed a boxed warning on Wyeth's Premarin, Prempro, and Premphase in early 2003 following the WHI randomized controlled trial (RCT), which evaluated one oral regimen of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) and was halted early after a prespecified interim analysis by the Data and Safety Monitoring Board found that overall health risks exceeded benefits.[2,3] Reported outcomes included increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis.[2,3] Soon thereafter, the FDA implemented class-wide labeling changes extending language about risks of serious adverse events observed in the WHI across all MHT products, including systemic and low-dose vaginal formulations.[4] The reasoning, per the 2003 FDA draft notice, was that "although only a single dose and type of estrogen and progestin were studied in the WHI, risks for serious adverse events should be assumed to be similar for other estrogens and progestins until data show otherwise."[4]

In November 2025, more than two decades later and after accumulation of long-term follow-up data and ad-

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ditional randomized and observational evidence clarifying that risks varied by age, timing, formulation, and route of administration, and that absolute risks were smaller while benefits were greater than initially perceived, the FDA requested the removal of boxed warning language for cardiovascular disease, breast cancer, and probable dementia from MHT while retaining the warnings for cardiovascular disease and breast cancer elsewhere for systemic products.[5] The boxed warning for endometrial cancer remains for systemic estrogen-alone products.[5]

FOOD AND DRUG ADMINISTRATION BOXED WARNINGS

Boxed warnings were developed to alert clinicians to serious adverse drug effects and to emphasize the need for clinical judgment when weighing risks and benefits. The FDA first introduced a boxed warning in 1961 for the antibiotic chloramphenicol, after routine label modifications failed to curb inappropriate prescribing despite the serious risk of aplastic anemia.[6] Boxed warnings were formally codified by the FDA in 1979, and they remain the strongest labeling precaution.[7] Boxed warnings appear as a prominent, black-bordered notice on drug labels intended to inform consumers, clinicians, and pharmacists on potential severe side effects. More than 400 medications have boxed warnings.[8] As of 2006, over 40% of patients in ambulatory clinical settings were prescribed at least one medication carrying a boxed warning.[8] This underscores that boxed warnings do not preclude use but instead signal the need for careful benefit-risk assessment. Importantly, there is no uniform evidentiary threshold for issuing a boxed warning. The MHT boxed warning was based on the results of a RCT, whereas other boxed warnings have been issued based on findings from observational studies, FDA's MedWatch voluntary reporting, or theoretical and mechanistic concerns. In practice, however, removal of a boxed warning often requires substantial confirmatory evidence and regulatory assessment.

WHY WAS MENOPAUSAL HORMONE THERAPY GIVEN A BOXED WARNING?

The WHI was the landmark RCT that informed the boxed warning and was subsequently applied broadly to all MHT products. On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs. placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect, and the global index statistic supported risks exceeding benefits.[3] After adjustment for multiple comparisons, reported hazard ratios (HRs) were 1.29 for coronary heart disease (adjusted 95% CI [aCI]: 0.85-1.97), 1.41 for stroke [aCI: 0.86-2.31], 2.13 for pulmonary embolism [aCI: 0.99-4.56], and 1.26 for breast cancer [aCI: 0.83-1.92].[3] In absolute terms, these findings corresponded to an additional seven, eight, eight, and 18 cases of coronary heart disease, stroke, breast cancer, and venous thromboembolism (VTE), respectively, per 10,000 women-years. Because the WHI evaluated only one oral CEE ± MPA regimen, extending a boxed warning to all hormone formulations and routes assumed a class effect that had not been established.

Although these absolute risks were small, and fall within the Council for International Organizations of Medical Sciences definition of "rare" adverse events (occurring between 1/10,000 and 1/1,000), the WHI data findings were released to the media before full peer review, resulting in headlines that exaggerated risks without context or consideration of benefits and generated widespread alarm.[9] Today, fewer than 5% of US women aged 52-65 years are prescribed MHT, even though more than 1.3 million women enter menopause annually and up to 80% will experience symptoms, despite strong evidence for its safety and efficacy.[10] The early perception of harm continues to dominate clinical practice and regulatory policy despite the fact that decades of follow-up studies have clarified and contextualized the risks.[11-14] For example, as outlined in point 1 through 5 below, subsequent randomized and observational evidence demonstrates clinically important heterogeneity in MHT risks and benefits by formulation, timing, and route of administration:

1. The WHI CEE-only arm did not show an increased risk of breast cancer, and long-term follow-up has suggested reduced breast cancer incidence and mortality.[15,16]
2. Observational studies suggest that estrogen combined with some synthetic progestins is associated with increased breast cancer risk, whereas estrogen combined with micronized progesterone has not been associated with increased risk.[17]
3. Post hoc WHI analyses found no increased cardiovascular risk among women younger than 60 years or within 10 years of menopause onset.[18]
4. Randomized trials including the Danish Osteoporosis Prevention Study and the Early Versus Late Intervention Trial With Estradiol, as well as meta-analyses, support the timing hypothesis, showing more favorable cardiovascular profiles with earlier initiation, including a reduction in all-cause mortality (relative risk: 0.70; 95% CI: 0.52-0.95).[19-21]
5. Thrombotic and stroke risks are type and route-dependent, with higher risk associated with synthetic progestins and oral CEE than oral estradiol.[22-25] Studies have shown that transdermal estradiol does not increase VTE or stroke risk.[26-28]

Furthermore, the 18-year WHI follow-up found no association between MHT and all-cause, cardiovascular, or cancer mortality (pooled HR: 0.99; 95% CI: 0.94-1.03).[29] These distinctions are clinically central to modern prescribing practices. Despite the evolving evidence base, the boxed warning for MHT persisted for an additional eight years following the WHI long-term follow-up.

CONTRASTED TIMELINES

The application and removal timeline of the MHT boxed warning stands in contrast to the application and

removal of the canagliflozin, a sodium-glucose cotransporter 2 inhibitor, boxed warning timeline (Fig. 1, timeline of MHT boxed warning and evidence versus timeline of canagliflozin and evidence).[2,3,5,15,17-21,29-35] The canagliflozin boxed warning provides an example of how the FDA can pivot rapidly when new data clarifies benefit-risk balance. Two RCTs published in 2017, Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal, demonstrated an increased risk of lower extremity amputation in the canagliflozin group versus the placebo group (6.3 vs 3.4 participants per 1,000 patient-years; HR: 1.97 [CI: 1.41-2.75]).[30,31] This data led to the FDA requiring a boxed warning for the risk of amputation in May 2017.[32] A subsequent study, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), was published in 2019 and demonstrated a 34% lower risk of adverse renal outcomes while having no signal for increased risk of amputation over 2.6 years.[33] In 2020, based on these new benefits and indications with lower than previously described risk of amputation, the FDA removed its boxed warning for canagliflozin after three years.[34] This removal is notable because the boxed warning was expeditiously removed. MHT, in contrast, despite multiple analyses and further RCTs demonstrating remarkable benefits and low risks in women within 10 years of menopause, had a boxed warning for 23 years. A key aspect of the boxed warning removal was that Janssen, the manufacturer of canagliflozin and supporter of CANVAS, CANVAS-R, and CREDENCE trials, was able to leverage the CREDENCE trial by filing a 2016 amendment to the trial that resulted in required foot exams at every visit, thus collecting important data that would prove or disprove the increased amputation risk.[36] The canagliflozin boxed warning timeline is compared with the MHT boxed warning timeline in Figure 1.

Figure 1 illustrates the timeline that boxed warnings can be dynamic when supported by regulatory processes that allow rapid incorporation of new evidence. The FDA demonstrated both responsiveness and proportionality: a boxed warning was applied when credible randomized evidence identified a serious safety signal and later removed it when subsequent evidence and updated benefit-risk assessment supported a more favorable profile. The example of canagliflozin illustrates that prolonged regulatory inertia is not inevitable; rather, it reflects the absence of a structured pathway for reassessing boxed warnings when the original assumptions underlying their application are no longer supported.

OTHER BOXED WARNING MEDICATION EXAMPLES

Another medication through which the impact of boxed warnings can be seen is varenicline (Chantix, Pfizer). Varenicline's boxed warning and subsequent decline in prescriptions with likely subsequent patient harm mirrors that of MHT. Two large RCTs demonstrated no serious psychiatric effects of varenicline with subsequent FDA approval for smoking cessation in 2006.[37-39] However, postmarketing data showed an increase in suicidal thoughts and aggressive behavior which prompted a boxed warning in 2009.[40] Following the boxed warning, prescribing declined substantially, with Veterans Affairs (VA) outpatient prescriptions decreasing by 69% within 12 months and by 82% when compared with 2008.[41] The boxed warning was removed in 2016 after the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) randomized trial found no significant increase in psychiatric or behavioral effects.[42] One year later, varenicline use had increased by 43% in VA patients. Reduced varenicline use during this period was associated with fewer successful smoking cessation attempts, with estimates suggesting up to 20,544 VA patients may not have quit smoking as a result.[41]

MHT followed a similar decline in prescriptions following the application of the boxed warning, dropping from 38.5% to 4.5% of women by 2020, with estimates up to 91,610 premature deaths among US women due to avoidance of estrogen therapy, primarily from preventable cardiovascular complications.[10,43] Beyond cardiovascular outcomes, osteoporosis-related morbidity is substantial: nearly 50% of postmenopausal women will experience an osteoporotic fracture during their lifetime.[44] Osteoporotic fractures are associated with pain, disability, loss of independence, and excess mortality, with approximately 20%-25% mortality within one year after hip fracture.[45] Osteoporosis-related fractures also impose a major economic burden in the United States, with direct medical costs estimated at roughly $17.9 billion annually.[46] MHT is FDA-approved for osteoporosis prevention and significantly reduces fracture risk, yet millions of women are diverted to less effective or poorly tolerated alternatives.[35,47]

Boxed warnings based on presumed class effects can be problematic when systemic exposure and biological plausibility differ across formulations. The boxed warning for TCIs, FDA-approved for atopic dermatitis, and low-dose vaginal estrogen provide two such examples. TCIs have had a boxed warning since 2006 for the concern of skin malignancy and lymphomas despite a reported lack of causal relationship in the warning itself.[48] This boxed warning originated from three pieces of evidence: (1) oral calcineurin inhibitors are used for immunosuppression typically after organ transplant and have a class effect boxed warning for malignancy and serious infection, (2) a study conducted in monkeys with oral doses of calcineurin inhibitors with subsequent blood levels 30 times higher than that seen in topical formulations found increased rates of lymphoma, and (3) rare cases of tumors in postmarketing data out of millions of topical prescriptions.[49,50] This boxed warning has continued for two decades despite a lack of evidence demonstrating a causal link between topical use and malignancy, greatly limiting dermatologists' treatment of atopic dermatitis.[51,52] Dermatologists have criticized the warning as biologically implausible and clinically harmful, given the minimal systemic absorption of topical formulations.[53]

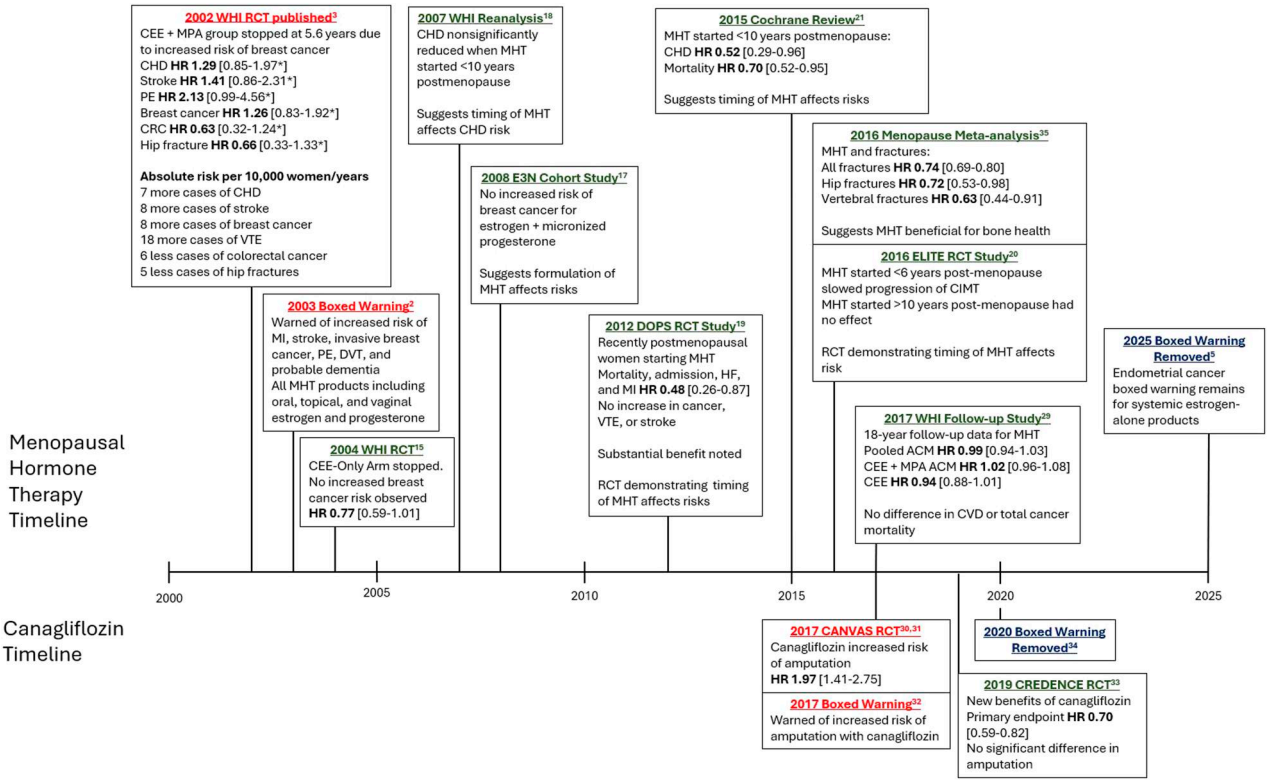

FIG. 1. Timeline of MHT boxed warning and evidence versus timeline of canagliflozin and evidence. ACM, all-cause mortality; CANVAS, Canagliflozin Cardiovascular Assessment Study; CEE, conjugated equine estrogen; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CRC, colorectal cancer; CVD, cardiovascular disease; DOPS, Danish Osteoporosis Prevention Study; DVT, deep vein thrombosis; ELITE, Early versus Late Intervention Trial with Estradiol; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; PE, pulmonary embolism; RCT, randomized controlled trial; WHI, Women's Health Initiative; VTE, venous thromboembolism.

Like oral and TCIs, low-dose vaginal estrogen received a boxed warning along with systemic MHT due to a class effect despite systemic estradiol levels being significantly different, and no human data of serious adverse outcomes from low-dose vaginal estrogen. In fact, at the time the WHI-driven boxed warnings were implemented, pharmacokinetic studies of vaginal estradiol tablets, including Vagifem (Novo Nordisc Bagsværd), suggested generally low systemic exposure, with serum estradiol typically remaining within or near postmenopausal ranges, although transient increases were sometimes reported with the initial 25 mcg loading dose.[54] Nonetheless, the FDA applied WHI-derived class-wide labeling across all MHT products, including formulations intended for local vulvovaginal and urinary symptoms. Given the biological plausibility that WHI risks were driven largely by systemic exposure to either estrogen-progesterone (breast cancer risk) and first-pass metabolism (VTE risk), extrapolating those risks to low-dose local vaginal estrogen, where systemic exposure is minimal and often transient, overstated potential harm. Therefore, it is biologically implausible, and evidence does not support that low-dose vaginal estrogen meaningfully increases the risk of long-term conditions such as breast cancer or cardiovascular disease.[55-57] The boxed warning should never have been applied to vaginal formulations. This distinction is clinically important given the established benefits of local vaginal estrogen for the genitourinary syndrome of menopause that affects more than half of postmenopausal women. Despite safety data, use of local estrogen remains low. A 2024 cost-analysis found annual urinary tract infection-related costs at $2 billion in the United States, with potential annual savings of $1,226-$4,888 per woman treated with vaginal estrogen.[58] In addition, a 2025 retrospective study of over one million women with recurrent UTIs found a 51% lower sepsis risk and 73% lower mortality among vaginal estrogen users.[59] These data reframe local estrogen as a public health intervention, reducing antibiotic use, infection, health care costs, and even mortality.

Members of the Working Group on Women's Health and Well-Being in Menopause, whose members are affiliated with organizations including The Menopause Society, the American College of Obstetricians and

Gynecologists, the Endocrine Society, the American Society for Reproductive Medicine, and the International Society for the Study of Women's Sexual Health, have endorsed low-dose vaginal estrogen as first-line therapy and contend that the boxed warning was not evidence-based and harmed women by discouraging use of a highly effective, low-risk treatment.[60] They advocated for revised labeling that clearly distinguished systemic hormone risks from low-dose vaginal estrogen.[60]

TRAINING GAPS AMONG PRIMARY CARE TRAINEES

A 2017 national survey of 183 internal medicine, family medicine, and OB/GYN residents found that while 94% agreed menopause management is important, only 7% felt adequately prepared.[61] Similarly, a single-institution study found that 81% of internal medicine residents reported limited menopause training, and around 80% felt uncomfortable managing female sexual response and dysfunction, and urinary incontinence and pelvic floor dysfunction, all of which have a huge impact on quality of life in women.[62] These training gaps are particularly consequential given the broad and multisystem manifestations of menopause. Large studies, including the Study of Women's Health Across the Nation, document associations between menopause and mood changes, sleep disturbance, joint pain, bone loss, cognitive complaints, and sexual dysfunction.[63] Yet, a recent publication[64] in a major family medicine journal reduced menopausal symptoms to vasomotor symptoms and vaginal dryness, overlooking well-established benefits of MHT on sleep, mood, and overall quality of life.[65,66] The same article continued to recommend MHT for the "shortest duration possible" and reported more harm than benefit, even among women aged 50-59, the group with the most favorable benefit-risk profile.[64] Given that this family medicine journal reaches more than 180,000 primary care providers, such outdated framing risks perpetuating the very misconceptions that drove the boxed warning and subsequent MHT underuse in primary care.

These challenges reflect not only individual knowledge gaps but also system-level training limitations. In a 2024 study of practicing providers, the most frequently cited barrier for managing menopausal symptoms was lack of training (62%), followed by patient safety concerns (52%).[67] Consistent with this, a 2022 survey of 145 US OB/GYN residency program directors, 93% agreed that standardized menopause curricula are needed, but only 31% had one in place.[68] Structured menopause education can improve knowledge and confidence, yet these models remain uncommon.[69,70] Because most menopausal care occurs in primary care settings, these educational gaps may limit access to evidence-based treatment and contribute to ongoing underuse of effective therapies. The boxed warning thus contributed not only to reduced utilization but also to erosion of menopause-related clinical confidence over time.

CLINICIANS AND ACADEMICS

Medical education should integrate menopause management into family medicine, internal medicine, and OB/GYN residency programs. Continuing medical education addressing both hormone and nonhormone therapies is necessary to inform, update, and equip providers. Interactive, clinically relevant education is most likely to translate into practice change.[67] Collaboration with menopause specialists and use of evidence-based guidelines can further support primary care clinicians managing MHT.[67] Another pivotal point is providing education focused on the removal of the FDA's boxed warnings on MHT. The 2025 labeling updates should be reflected in training and continuing education. Patient information needs to reflect long-term follow-up data, such as findings from Chlebowski et al,[16] demonstrating a reduction in breast cancer risk in the WHI within the estrogen-only arm. Decision-support tools within electronic health records may help clinicians apply updated evidence in individualized care.

CONCLUSION

The removal of the boxed warning marks an inflection point. Action at every level, including regulatory, clinical, academic, and research, will promote evidence-based rather than fear-based menopausal care. A recent call to geriatricians advocates for translating policy to practice with updated prescribing habits for MHT.[71]

The original class-wide warning was based on evidence from specific regimens studied in the WHI. The science underlying the original class-wide warning is outdated. The WHI demonstrated that use of CEE ± MPA, in a population of predominantly older postmenopausal women (mean age: 63 y) with baseline risk factors for cardiovascular disease and breast cancer, resulted in small absolute increases in several adverse outcomes.[3] It did not establish uniform risk across all hormone formulations, progestogens, doses, routes of administration, or age groups. Subsequent trials, extended follow-up, and observational studies demonstrate that outcomes vary meaningfully by age, timing of initiation, formulation, and route of administration.[15,17-20,26-28]

The FDA should establish a standardized, transparent boxed warning algorithm that includes defined evidentiary thresholds for initiation and removal, mandatory periodic reassessment, formulation and route-specific labeling, clear acknowledgment of uncertainty and heterogeneity, and incorporation of absolute risk estimates. Such a framework would ensure that boxed warnings evolve with the science, preserve biological plausibility, and support informed, individualized clinical decision making rather than perpetuating overly broad or outdated risk messaging. For example, for clinicians and patients, there is a profound difference between the boxed warning stating "increases breast cancer risk" as opposed to the actual number of "eight additional cases per 10,000 women per year" when making a shared decision on whether to start MHT.

Boxed warnings influence clinician confidence, patient perceptions, medical education, and health system behavior, and therefore have effects beyond pharmacovigilance. The MHT boxed warning contributed to sustained underutilization of one of the most effective therapies in women's health, to erosion of menopause training in primary care, and potentially to avoidable morbidity and mortality related to cardiovascular disease, fractures, genitourinary infections, and diminished quality of life. For women with bothersome menopausal symptoms or elevated fracture risk, the potential benefits of appropriately selected MHT can be substantial, whereas absolute risks, particularly in younger women and with transdermal or body-identical formulations, are low. Delayed reassessment of safety communications can influence care patterns and patient access. Removal of the boxed warning aligns labeling with contemporary evidence and biological understanding.

For clinicians and educators, this change offers an opportunity to reframe menopause care. Future research must move beyond broad questions of whether MHT is "safe" or "unsafe" and instead focus on comparative effectiveness and formulation-specific outcomes. The 2025 labeling updates should be incorporated into continuing education and clinical guidance.[1] Patient counseling needs to reflect long-term follow-up data, such as findings from Chlebowski et al,[16] demonstrating a reduction in breast cancer risk in the WHI within the estrogen-only arm. The Menopause Society's current guidance no longer recommends using hormone therapy at the "lowest dose for the shortest duration," and instead emphasizes individualized care, noting that MHT may be continued as long as benefits outweigh risks.[72] Treatment should instead be tailored to individual health status, symptom burden, and personal goals. For some women, long-term use may be appropriate for persistent menopausal symptoms or osteoporosis prevention. Furthermore, primary care empowerment is critical as family physicians and internists are well-positioned to manage menopausal symptoms safely and effectively.

REFERENCES

1. U.S. Food and Drug Administration *HHS Advances Women's Health, Removes Misleading FDA Warnings on Hormone Replacement Therapy*. Silver Spring (MD): FDA; 2025. Accessed January 24, 2026. https://www.fda.gov/news-events/press-announcements/hhs-advances-womens-health-removes-misleading-fda-warnings-hormone-replacement-therapy
2. Jeffrey S. Estrogen formulations get FDA "black-box" Warning. *Medscape*. 2003. Accessed January 24, 2026. https://www.medscape.com/viewarticle/785840#vp_2?form = fpf
3. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002;288:321-333. doi:10.1001/jama.288.3.321
4. U.S. Food and Drug Administration. Docket No. 98D-0834 Draft Guidance for Industry on Labeling for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling; Availability; Silver Spring (MD): FDA; Federal Register Vol. 68 (22). 2003. Accessed January 24, 2026.
5. U.S. Food and Drug Administration *FDA Requests Labeling Changes Related to Safety Information to Clarify the Benefit/Risk Considerations for Menopausal Hormone Therapies*. Silver Spring (MD): FDA; 2025.
6. National Library of Medicine. Daily Med. Chloramphenicol Sodium Succinate. FDA Drug Label [Internet] 2024-10-10. Accessed January 24, 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid = aed29594-211d-49ef-813f-131975a8d0e3
7. U.S. Food and Drug Administration *Drug Therapies and Regulation in the US*. Silver Spring (MD): FDA; 2023.
8. Wagner AK, Chan KA, Dashevsky I, et al. FDA drug prescribing warnings: is the black box half empty or half full? *Pharmacoepidemiol Drug Saf* 2006;15:369-386. doi:10.1002/pds.1193
9. Council for International Organizations of Medical Sciences (CIOMS) *Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition: Report of CIOMS Working Groups III and V*. Geneva: CIOMS; 1999. ISBN 92 9036 070 4. Accessed February 9, 2026. https://cioms.ch/wp-content/uploads/2018/03/WG3_Guidelines-for-Preparing-Core-Clinical-Safety-Information-on-Drugs.pdf
10. Yang L, Toriola A. Menopausal hormone therapy use among postmenopausal women. *JAMA Health Forum* 2024;5:e243128. doi:10.1001/jamahealthforum.2024.3128
11. Langer RD. The evidence base for HRT: what can we believe? *Climacteric* 2017;20:91-96. doi:10.1080/13697137.2017.1280251
12. Langer RD, Hodis HN, Lobo RA, Allison MA. Hormone replacement therapy - where are we now? *Climacteric* 2021;24:3-10. doi:10.1080/13697137.2020.1851183
13. Stute P, Marsden J, Salih N, Cagnacci A. Reappraising 21 years of the WHI study: putting the findings in context for clinical practice. *Maturitas* 2023;174:8-13. doi:10.1016/j.maturitas.2023.04.271
14. Levy B, Simon JA. A contemporary view of menopausal hormone therapy. *Obstet Gynecol* 2024;144:12-23. doi:10.1097/AOG.0000000000005553
15. Anderson GL, Limacher M, Assaf AR, et al. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712. doi:10.1001/jama.291.14.1701
16. Chlebowski R, Anderson G, Aragaki A, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative Randomized Clinical Trials'. *JAMA* 2020;324:369-380. doi:10.1001/jama.2020.9482
17. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103-111. doi:10.1007/s10549-007-9523-x
18. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477. doi:10.1001/jama.297.13.1465
19. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *Brit Med J* 2012;345:e6409. doi:10.1136/bmj.e6409
20. Hodis H, Mack W, Henderson V, et al. ELITE research group. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;374:1221-1231. doi:10.1056/NEJMoa1505241
21. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev* 2015;2015:CD002229. doi:10.1002/14651858.CD002229
22. Hipolito Rodrigues MA, Gompel A. Micronized progesterone, progestins, and menopause hormone therapy. *Women Health* 2021;61:3-14. doi:10.1080/03630242.2020.1824956
23. Shifren J, Rifai N, Desindes S, McIlwain M, Doros G, Mazer N. A comparison of the short-term effects of oral conjugated equine estrogens versus transdermal estradiol on C-reactive protein, other serum markers of inflammation, and other hepatic proteins

in naturally menopausal women. *J Clin Endocrinol Metab* 2008; 93:1702-1710. doi:10.1210/jc.2007-2193
24. Chang WC, Wang JH, Ding DC. Conjugated equine estrogen used in postmenopausal women associated with a higher risk of stroke than estradiol. *Sci Rep* 2021;11:10801. doi:10.1038/s41598-021-90357-6
25. Smith NL, Blondon M, Wiggins KL, et al. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern Med* 2014;174:25-31. doi:10.1001/jamainternmed.2013.11074
26. Scarabin P, Oger E, Plu-Bureau G, EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432. doi:10.1016/S0140-6736(03)14066-4
27. Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. *Stroke* 2016;47:1734-1741. doi:10.1161/STROKEAHA.116.013052
28. Løkkegaard E, Nielsen L, Keiding N. Risk of stroke with various types of menopausal hormone therapies: a national cohort study. *Stroke* 2017;48:2266-2269. doi:10.1161/STROKEAHA.117.017132
29. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. *JAMA* 2017;318: 927-938. doi:10.1001/jama.2017.11217
30. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-657. doi:10.1056/NEJMoa1611925
31. Erondu N, Shaw W, Barrett TD, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018;9: 691-704. doi:10.1016/S2213-8587(18)30141-4
32. U.S. Food and Drug Administration *FDA Drug Safety Communication: FDA Confirms Increased Risk of Leg and Foot Amputations With the Diabetes Medicine Canagliflozin (Invokana, Invokamet, Invokamet XR)*. Silver Spring (MD): FDA; 2020. Accessed January 24, 2026. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-confirms-increased-risk-leg-and-foot-amputations-diabetes-medicine
33. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE trial investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295-2306. doi:10.1056/NEJMoa1811744
34. U.S. Food and Drug Administration *FDA Drug Safety Communication: FDA removes Boxed Warning About Risk of Leg and Foot Amputations With The Diabetes Medicine Canagliflozin (Invokana, Invokamet, Invokamet XR) [Internet]*. Silver Spring (MD): FDA; 2020. Accessed January 24, 2026. https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin
35. Zhu L, Jiang X, Sun Y, Shu W. Effect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomized controlled trials. *Menopause* 2016;23:461-470. doi:10.1097/GME.0000000000000519
36. Melillo G FDA removes canagliflozin's boxed warning for amputation. *Am J Manag Care* 2020. Accessed January 24, 2026: https://www.ajmc.com/view/fda-removes-canagliflozin-s-boxed-warning-for-amputations
37. Jorenby DE, Hays JT, Rigotti NA, et al. Varenicline phase 3 study group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56-63. doi:10.1001/jama.296.1.56
38. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an α4β2 Nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled Trial. *JAMA* 2006;296:47-55. doi:10.1001/jama.296.1.47
39. U.S. Food and Drug Administration *Drug Approval Package: Chantix (Varenicline)*. Silver Spring (MD): FDA; 2025. Drug Approval Package: Chantix (Verenicline) NDA #021928. Accessed January 24, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/021928orig1s040.pdf
40. Davies NM, Thomas KH. The Food and Drug Administration and varenicline: should risk communication be improved? *Addiction* 2017;112:555-558. doi:10.1111/add.13592
41. Desai RJ, Good MM, San-Juan-Rodriguez A, et al. Varenicline and nicotine replacement use associated with US Food and Drug Administration Drug Safety Communications. *JAMA Netw Open* 2019;2:e1910626. doi:10.1001/jamanetworkopen.2019.10626
42. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-2520. doi:10.1016/S0140-6736(16)30272-0
43. Sarrel P, Njike V, Vinante V, Katz D. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health* 2013;103:1583-1588. doi:10.2105/AJPH.2013.301295
44. Keen MU, Barnett MJ, Anastasopoulou C. Osteoporosis in females. 2025. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2025. PMID: 32644582. https://www.ncbi.nlm.nih.gov/books/NBK559156/
45. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture - a systematic review. *World J Orthop* 2019;10:166-175. doi:10.5312/wjo.v10.i3.166
46. Clarke BL. Economic costs of severe osteoporotic fractures continue to increase at expense of refracture. *J Bone Min Res* 2022;37: 1809-1810. doi:doi.org/10.1002/jbmr.4713
47. Silva BC, Hipólito Rodrigues MA. Estrogen hormone therapy and postmenopausal osteoporosis: does it really take two to tango? *Women Health* 2023;63:770-773. doi:10.1080/03630242.2023.2278211
48. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. *Am J Clin Dermatol* 2013;14:163-178. doi:10.1007/s40257-013-0020-1
49. National Library of Medicine. Daily Med. Prograf. FDA Drug Label. Updated date: 2023-08-25. Accessed January 24, 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid = 7f667de1-9dfa-4bd6-8ba0-15ee2d78873b
50. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-132. doi:10.1016/j.jaad.2014.03.023
51. Leung A, Bhutani T, Brownstone N, Koo J. FDA boxed warnings: should package inserts include levels of evidence? *J Drugs Dermatol* 2025;24:e67-e69. doi:10.36849/JDD.9122
52. Ceilley R, Eisenthal A. The unintended effects of a boxed warning. *J Clin Aesthet Dermatol* 2009;2:33-39. PMID: 20729957.
53. Lam M, Zhu JW, Tadrous M, Drucker AM. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. *JAMA Dermatol* 2021;157:549-558. doi:10.1001/jamadermatol.2021.0345
54. Archer DF, Constantine GD, Simon JA, et al.; REJOICE Study Group. TX-004HR vaginal estradiol has negligible to very low systemic absorption of estradiol. *Menopause* 2017;24:510-516. doi:10.1097/GME.0000000000000790
55. Crandall CJ, Diamant A, Santoro N. Safety of vaginal estrogens: a systematic review. *Menopause* 2020;27:339-360. doi:10.1097/GME.0000000000001468
56. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause* 2018;26:603-610. doi:10.1097/GME.0000000000001284
57. Pavlović RT, Janković SM, Milovanović JR, et al. The safety of local hormonal treatment for vulvovaginal atrophy in women with estrogen receptor-positive breast cancer who are on adjuvant aromatase inhibitor therapy: Meta-analysis. *Clin Breast Cancer* 2019;19:e731-e740. doi:10.1016/j.clbc.2019.07.007
58. Houston C, Azar W, Huang S, Rubin R, Dorris C, Sussman R. A cost savings analysis of topical estrogen therapy in urinary tract infection prevention among postmenopausal women. *Urol Pract* 2024;11:257-266. doi:10.1097/UPJ.0000000000000513

59. Wells B, Visingardi J, Feustel P, De E. Impact of vaginal estrogen on serious adverse outcomes in postmenopausal women with recurrent urinary tract infections: a retrospective study. *Continence* 2025;15S:102042. doi:10.1016/j.cont.2025.102042
60. Manson J, Goldstein SR, Kagan R, et al. for the working group on women's health and well-being in menopause. why the product labeling for low-dose vaginal estrogen should be changed. *Menopause* 2014;21:911-916. doi:10.1097/GME.0000000000000316
61. Kling J, MacLaughlin K, Schnatz P, et al. Menopause management knowledge in postgraduate family medicine, internal medicine, and obstetrics and gynecology residents: a cross-sectional survey. *Mayo Clin Proc* 2019;94:242-253. doi:10.1016/j.mayocp.2018.08.033
62. Hsieh E, Nunez-Smith M, Henrich J. Needs and priorities in women's health training: perspectives from an internal medicine residency program. *J Women's Health (Larchmt)* 2013;22:667-672. doi:10.1089/jwh.2013.4264
63. El Khoudary S, Greendale G, Crawford S, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2019;26:1213-1227. doi:10.1097/GME.0000000000001424
64. Fugh-Berman A, Mintzes B. Menopausal hormone therapy: limited benefits, significant harms. *Am Fam Physician* 2025;112:15-16.
65. Pan Z, Wen S, Qiao X, Yang M, Shen X, Xu L. Different regimens of menopausal hormone therapy for improving sleep quality: a systematic review and meta-analysis. *Menopause* 2022;29:627-635. doi:10.1097/GME.0000000000001945
66. Liu Q, Huang Z, Xu P. Effects of hormone replacement therapy on mood and sleep quality in menopausal women. *World J Psychiatry* 2024;14:1087-1094. doi:10.5498/wjp.v14.i7.1087
67. Jeevananthan A, Alexopoulos AS, Goldstein KM, Moreno AC. Perceptions of menopause care: a pilot survey study of providers from primary care, endocrinology, and obstetrics and gynecology. *J Womens Health (Larchmt)* 2025;34:1462-1471. doi:10.1177/15409996251370925
68. Allen J, Laks S, Zahler-Miller C, et al. Needs assessment of menopause education in United States obstetrics and gynecology residency training programs. *Menopause* 2023;30:1002-1005. doi:10.1097/GME.0000000000002234
69. Christmas M. It is time to standardize menopause curriculum in residency. *Menopause* 2023;30:993-994. doi:10.1097/GME.0000000000002247
70. Christianson M, Washington C, Stewart K, Shen W. Effectiveness of a 2-year menopause medicine curriculum for obstetrics and gynecology residents. *Menopause* 2016;23:275-279. doi:10.1097/GME.0000000000000531
71. Hanfling S, Vereecken SJ, MacRae K, Rubin R. FDA boxed warning removal on menopause hormone therapy: what geriatricians should know. *J Am Geriatr Soc* 2025. doi:10.1111/jgs.70256
72. Allen RH, Amanam I, Anderson DN, et al. *Menopause Practice: A Clinician's Guide*, 6th edn. Pepper Pike, Ohio: North American Menopause Society; 2019.

