Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Estrogen-Containing Menopausal Hormone Therapy

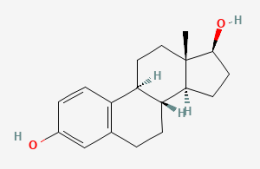
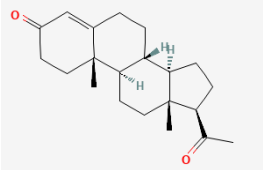
Evidence Summary

When initiated close to the time of menopause, mHT has null effects on cognitive functions, decreases coronary heart disease risk, increases bone density, and slightly increases breast and ovarian cancer risk.

Neuroprotective Benefit: When initiated within 10 years of menopause or under age 60, mHT has neutral effects on cognitive functions. When initiated 10 years after menopause or above age 65, estrogen-progestogen formulations may increase dementia risk.

Aging and related health concerns: mHT reduces vasomotor symptoms and increases bone density but slightly increases risks for breast and ovarian cancer. Risk of venous thromboembolism varies based on mHT formulations and route.

Safety: Risks of mHT varies by type, dose, route, timing of initiation, treatment duration, and medical history. Estrogen-progestogen mHT slightly increases breast and ovarian cancer risk. Venous thromboembolism risk varies by route and formulations.

Availability: Rx	**Dose**: active ingredients and doses vary across products; route also varies from oral, transdermal, and vaginal	**Chemical structures:**  Estradiol: $C_{18}H_{24}O_2$; MW=272.4  Progesterone: $C_{21}H_{30}O_2$; MW=314.5
Half-life: half-life of oral estradiol is 13-20 hours; half-life of transdermal estradiol is 2.7 hours (after removal of transdermal patch); half-life of oral micronized progesterone is ~5 hours	**BBB**: penetrant	
Clinical trials: A 2025 Cochrane meta-analysis included a total of 45,660 participants from double-blind randomized controlled trials.	**Observational studies**: Meta-analyses of observational studies have included 4+ million participants.	

What is it?

Menopausal hormone therapy (mHT) replaces estrogen (and progesterone if appropriate) lost during menopause and is approved for the treatment of hot flashes and night sweats. Menopause is a natural part of aging that occurs in women between 45-55 years of age, when a woman's body stops menstruating and the ovaries stop producing estrogens and progesterone. A woman has officially experienced menopause once she has gone 12 months without menstruating. This clear-cut threshold is preceded by years of "perimenopause" with irregular cycles, fluctuating estrogen levels, decreased progesterone levels, and other symptoms. The variability and loss of ovarian hormones during perimenopause and menopause can trigger natural changes like hot flushes, vaginal dryness, mood and memory symptoms, and other changes. The experiences vary widely across women. Most menopausal symptoms can be effectively treated by carefully managed mHT [1].

The term "estrogens" refers not to a single molecule but rather to a class of diverse molecules that can affect the estrogen receptors. Before menopause, the primary estrogen created by the ovary is 17β-estradiol. Other natural estrogens in a woman's body include estrone, estriol, and 17α-estradiol. After menopause, the levels of circulating 17β-estradiol fall below that of most men and the primary estrogen in circulation switches to estrone, synthesized from adrenal steroids. mHT usually consists of estrogens

alone (e.g., in women who have undergone a hysterectomy) or estrogens combined with a progestogen (in women with a uterus). Many types of mHTs exist. Menopausal women can experience typically mild problems with their memory and mental abilities but these changes are transient, often disappearing within a couple of years [2].

In 2002, the Women's Health Initiative (WHI) Study reported that in 16,000+ postmenopausal women over the age of 65, mHT increased the risk of dementia, breast cancer, heart disease, stroke, and venous thromboembolism [3; 4]. However, caveats and controversies were raised regarding the timing of the mHT (initiation more than 10 years past menopause) and the formulations used—conjugated equine estrogens and a synthetic progesterone, medroxyprogesterone acetate (MPA), versus bioidentical hormone therapies. Much debate and research ensued. In July 2025, the FDA removed the boxed warnings (cardiovascular disease, stroke, breast cancer, probable dementia) of all combined estrogen-progestogen products as well as estrogen-alone and progestogen-alone products [5]. Recommendation to prescribe mHT "at the lowest effective dose for the shortest duration" has also been removed. New labels include updated guidance on initiating treatment in women younger than 60 years old or within 10 years of menopause onset to optimize benefit-to-risk balance.

Neuroprotective Benefit: When initiated within 10 years of menopause or under age 60, mHT has neutral effects on cognitive functions. When initiated 10 years after menopause or above age 65, estrogen-progestogen formulations may increase dementia risk.

Types of evidence:

- 5 meta-analyses or systematic reviews
- 6 randomized clinical trials
- Numerous observational studies
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

While estrogen-containing mHT can be used for treating some menopausal symptoms like hot flushes, it is not recommended for preventing cognitive aging or dementia [1]. For most women undergoing natural menopause, the use of mHT appears to have a neutral effect on cognitive functions [6; 7; 8]. However, in premenopausal women who undergo oophorectomy, the use of estrogen therapy is

associated with a lower risk of dementia [1]. In women over 65 years of age, starting treatment with estrogens plus progestins can increase the risk of dementia, based on evidence from the WHI study [4; 9].

mHT has a long history of research for its potential cognitive benefits and protective effects against dementia. Below are some key individual clinical trials.

Women's Health Initiative Memory Study (WHIMS)

The Women's Health Initiative Memory Study (WHIMS) was the largest clinical trial carried out to date that tested the efficacy of mHT on preventing cognitive decline and dementia; this study was an ancillary study of the Women's Health Initiative, which assessed the health benefits and risks of mHT. In 2002, the large double-blind placebo-controlled clinical trial reported that in 4,532 postmenopausal women over the age of 65, mHT treatment (0.625 mg of conjugated equine estrogens with or without 2.5 mg of medroxyprogesterone acetate [MPA] per day) for 5.2 years increased the risk of dementia (HR=2.05, 95% CI, 1.21 to 3.48)[4]. In addition, an MRI study showed that women receiving mHT (either conjugated estrogens alone or with MPA) had greater atrophy of the frontal lobe and hippocampal volume compared to placebo [10]. Treatment effects on mild cognitive impairment did not differ between mHT and placebo groups.

It is worth highlighting that study participants in the WHIMS were, on average, 72 years old and approximately 15 years post-menopause when they initiated mHT, possibly beyond the therapeutic window of hormone therapy efficacy. Additionally, there are controversies regarding the formulations used in the WHIMS—conjugated equine estrogens and a synthetic progesterone (MPA), versus bioidentical hormone therapies available now. Subsequent studies have tested one or both of these questions.

Women's Health Initiative Memory Study of Younger Women (WHIMSY)

The Women's Health Initiative Memory Study of Younger Women (WHIMSY) tested whether prescribing oral conjugated equine estrogens with or without progestogen to postmenopausal women aged 50 to 55 years has long-term effects on cognitive function. In the randomized placebo-controlled trial of 1,326 postmenopausal women, mHT (0.625 mg of oral conjugated equine estrogens alone or with 2.5 mg of MPA per day) for 7 years resulted in global cognitive function scores that were similar to those in the placebo group [11]. Similarly, no significant differences between mHT and placebo groups were found in

individual cognitive domain scores. Prespecified subgroup analyses found that mHT may have adversely affected verbal fluency in women who had a prior hysterectomy or prior use of mHT, though the authors noted that these may have been chance findings.

Kronos Early Estrogen Prevention Study (KEEPS)

KEEPS was a randomized placebo-controlled clinical trial that enrolled 727 women who were within 3 years of menopause and had good cardiovascular heath (average age of 52.6 years at the start of the study) [7]. Participants were randomized to either oral synthetic estrogen (conjugated equine estrogens; Premarin, 0.45 mg/day), transdermal bioidentical estrogen (17β-estradiol; Climara, 50 µg/day), or placebo, combined with progesterone (Prometrium, 200 mg/day; capsule taken orally daily for 12 days at the beginning of each month). The intervention lasted for 4 years. At the end of the intervention, cognitive functions, measured using a battery of 11 cognitive tests, were not different in women who received either form of mHT compared to those who received placebo. Cognitive tests included those that assessed verbal learning and memory, auditory attention, working memory, visual attention, executive function, speeded language, and mental flexibility.

In the KEEPS Continuation Study, 299 participants from the original KEEPS were re-evaluated approximately 10 years after the end of the mHT/placebo intervention [6]. Cognitive assessments from the original KEEPS were repeated for the KEEPS Continuation Study, including the same battery of 11 cognitive tests. Ten years after the end of the intervention, women who received either form of mHT did not experience better or worse cognitive outcomes compared to those who received placebo. In the same Continuation study, neither form of mHT significantly affected Aβ load (measured by amyloid PET) or structural MRI biomarkers (hippocampal atrophy, dorsolateral prefrontal cortex thickness) compared to placebo 10 years after the end of the intervention [12]. APOE4 status did not modify the findings.

Early vs Late Intervention Trial with Estradiol (ELITE)

The Early vs Late Intervention Trial with Estradiol (ELITE) randomized controlled trial enrolled 567 healthy women to compare the effects of mHT in people within 6 years versus those over 10 years after menopause. Treatment with oral 17β-estradiol (1 mg/day) and cyclic micronized progesterone (vaginal gel, once daily for 10 days per 30-day cycle) for 5 years did not benefit or harm cognitive abilities such as verbal memory, executive functions, and global cognition, whether the treatment was initiated early (within 6 years) or late (after 10 years) [8].

Totality of evidence from select recent meta-analyses and systematic reviews:

In a 2024 meta-analysis of 34 randomized controlled trials including a total of 14,914 mHT-treated and 12,679 placebo participants, mHT had no overall effects on cognitive domain scores [9]. For natural menopause, estrogen-progestogen therapy was associated with a decline in cognitive functions (measured by the MMSE) as compared to placebo, which was driven by most studies administering treatment in a late-life population. In an analysis of timing of mHT initiation, mHT therapy during midlife showed no significant effects on global cognition, while mHT in late-life was associated with mild reductions in global cognition (p=0.004). When initiated specifically in midlife or close to menopause onset, estrogen-only therapy was associated with improved verbal memory (p=0.046), while late-life initiation had no effects. With regards to duration of mHT treatment, the meta-analysis found no changes in cognitive domain scores with shorter duration of mHT and a worsening in visual memory with longer treatment duration (p=0.022). In women who had undergone surgical menopause (induced by surgical removal of ovaries), estrogen-only therapy improved global cognition (p=0.043) compared to placebo.

In a 2023 meta-analysis of 4 randomized controlled trials of postmenopausal women over the age of 65, mHT use resulted in an increased risk of dementia (RR=1.38; 95% CI, 1.16 to 1.64, p<0.001), driven by the oral conjugated equine estrogens + MPA formulation (RR=1.64, 95% CI, 1.20 to 2.25; p=0.002) while no significant effect was seen with the estrogens-only therapy [13]. In the same report, a meta-analysis of 45 observational studies was performed and found that mHT use is associated with a lower risk of Alzheimer's disease (RR=0.78; 95% CI, 0.64 to 0.95, p=0.013) and all-cause dementia (RR=0.81; 95% CI, 0.70 to 0.94, p=0.007). It is worth noting that observational studies are designed to show associations and are not designed to prove cause versus effect. Protective associations were seen with estrogens-only therapy, typically taken in women with prior hysterectomy (RR=0.86; 95% CI, 0.77 to 0.95; p=0.002), but not with estrogens-progestogen therapy. Midlife estrogens-only mHT was associated with a 32% lower risk of dementia (RR=0.69; 95% CI, 0.51 to 0.92; p=0.010), while midlife estrogens-progestogen mHT was associated with a numerically, but not statistically, lower risk of dementia (RR=0.78; 95% CI, 0.47 to 1.27). Late-life mHT use was associated with a numerically, but not statistically, higher dementia risk.

In a 2025 meta-analysis of 10 mostly observational studies (1 randomized controlled trial and 9 observational studies), no significant association was found between mHT use and risk of mild cognitive impairment or dementia [14]. Subgroup analyses by timing of intervention, duration of therapy, and type of mHT showed no significant effects. There were insufficient data to evaluate whether the route of

delivery (oral, transdermal, intrauterine), type of estrogen, type of progestogen, or dose modifies the risk of mild cognitive impairment or dementia.

In a 2020 meta-analysis of up to 26 observational studies, no overall relationship between mHT and Parkinson's disease was found (OR=1.14, 95% CI, 0.95 to 1.38), but subgroup analysis showed a significant relationship between Parkinson's disease and progestogen use (OR=3.41; 95% CI, 1.23 to 9.46) or estrogen-progestogen use (OR=1.49, 95% CI, 1.34 to 1.65)[15]. Estrogen-only formulations did not have significant associations with Parkinson's disease (OR=1.08; 95% CI, 0.90 to 1.22). The relationship between mHT use and Parkinson's disease was significant only in cohort studies (OR=1.39; 95% CI, 1.28 to 1.52) and not in case-control studies (OR=0.96; 95% CI, 0.74 to 1.26).

Human research to suggest benefits to patients with dementia:

In a 2020 meta-analysis of 4 double-blind randomized controlled trials including a total of 277 Alzheimer's patients, mHT significantly improved one cognitive score (ADAS-Cog) based on 2 trials, while no significant effects of mHT were seen in another cognitive score (MMSE) based on 3 trials or the Clinical Dementia Rating scale based on 2 trials [16]. The included clinical trials were small in size and varied in mHT formulations (conjugated equine estrogens in 3 studies, estradiol + norethisterone in 1 study) and duration (4-12 months), and therefore the effects of mHT in Alzheimer's patients are considered inconclusive.

A 2009 Cochrane meta-analysis has also reported that estrogen-containing mHT does not improve cognition or function in Alzheimer's disease patients [17].

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Some observational studies have explored the relationships between mHT use and biomarkers of Alzheimer's disease; however, findings have been inconclusive given these studies are not designed to prove cause versus effect. There are many confounding factors related to observational research. One confounder is the "healthy-user" bias suggesting that women who choose to use mHT share other healthy characteristics that positively affect brain health. The opposite can also be true, where women who choose to use mHT may have more severe menopausal vasomotor symptoms, which themselves can relate to greater brain Aβ pathology [18]. Observational findings related to tau pathology have been mixed, with some studies suggesting that mHT is associated with greater tau accumulation [19], while others suggest less tau pathology [20; 21].

Estrogens and progestogens have many complex actions in the brain. Based on vast amounts of literature, estrogens can improve energy production, reduce oxidative stress, increase brain cell survival during damage, enhance the release of protective chemicals like growth factors, and improve memory by strengthening the connections between brain cells (reviewed in [22]). However, estrogens can also be harmful, and the type and timing of treatment can be important. Laboratory experiments suggest that estrogens protect healthy cells from new damage but can harm neurons that are already unhealthy [23]. The timing, duration, and type of treatment can similarly change whether estrogens will protect or exacerbate injury in models of stroke [24]. Progestogens can sometimes block the protective effects of estrogens but they can also be protective themselves – the effects appear to depend on the type of progestogen, the timing and the type of treatment and injury, and other variables [25].

APOE4 interactions:

The literature is mixed and inconsistent regarding the relationship between the effects of mHT and APOE genotype, with some studies showing no interactions, others showing potential benefit of mHT in APOE4 carriers compared to non-carriers, and others showing potential harm in APOE4 carriers. For example, the KEEPS study found no differences between APOE4 carriers and non-carriers regarding cognitive effects of a 4-year mHT intervention (oral conjugated equine estrogens or transdermal estradiol with or without progesterone) [7]; there were also no differences based on APOE genotype in long-term changes in Aβ load, hippocampal atrophy, or dorsolateral prefrontal cortex thickness [12]. In a longitudinal cohort of 136 cognitively unimpaired women, APOE4 carriers who were mHT users showed worse cerebral spinal fluid (CSF) levels of p-tau181/Aβ42 and Aβ42/40 ratios than non-carrier mHT users and non-users (regardless of genotype) [26]. In this study, younger age at mHT initiation was associated with worse levels of CSF p-tau181/Aβ42 and Aβ42/40 ratios in APOE4 carriers but not in non-carriers. In a European longitudinal cohort, mHT produced more cognitive benefits in APOE4 carriers, performing better in delayed memory tasks (RBANS) and having larger entorhinal and amygdala volumes than non-mHT users [27]. In this cohort, earlier mHT initiation was associated with a larger hippocampal volume, an association that was only observed in APOE4 carriers.

Aging and related health concerns: mHT reduces vasomotor symptoms and increases bone density but slightly increases risks for breast and ovarian cancer. Risk of venous thromboembolism varies based on mHT formulations and route.

Types of evidence:

- 23 meta-analyses or systematic reviews
- 1 systematic review and recommendations from the International Menopause Society
- Numerous observational studies
- Numerous laboratory studies

Menopausal symptoms: DECREASED VASOMOTOR SYMPTOMS

In 2025, the International Menopause Society performed a rigorous systematic review and produced detailed new recommendations related to women's midlife health, menopause, and mHT [1]. Recommendations were developed by 38 experts and 26 support team members, with oversight from a publication steering committee. Based on their recommendations, mHT is the most effective treatment for vasomotor symptoms and should be offered to women with bothersome vasomotor symptoms who do not have significant contraindications and are not averse to mHT. For the treatment of vasomotor symptoms, mHT is recommended to women younger than 60 years old or within 10 years of menopause, after full evaluation of benefits and risks. Low to moderate doses of mHT, including oral or transdermal formulations, alleviate symptoms in more than 80% of postmenopausal women. Estrogen-only therapy is recommended for women without an intact uterus, while an estrogen–progestogen combination is recommended for women with an intact uterus.

Based on a 2025 meta-analysis of randomized controlled trials, mHT improves menopause-related quality of life in women experiencing bothersome menopausal symptoms [28].

Bone density: INCREASED BONE DENSITY; DECREASED RISK OF FRACTURES

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT decreased the risk of all clinical fractures (from 111 to 87 women in every 1000; RR=0.78, 95% CI, 0.71 to 0.86), but this was based on 1 large study (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29]. Estrogen-only mHT in women who had undergone hysterectomy also decreased all clinical fractures (RR=0.73, 95% CI, 0.65 to 0.80).

A 2025 meta-analysis of randomized controlled trials reported that mHT significantly improved lumbar bone density compared to controls [28]. When examining the different mHT formulations separately, estradiol plus norethindrone acetate, estradiol-alone, and conjugated equine estrogen/estradiol significantly improved hip bone density compared to control.

Based on the 2025 recommendations from the International Menopause Society, mHT is the first-line therapy for the prevention of menopause-related bone loss [1]. mHT significantly reduces the risk of osteoporosis-related fractures. Benefits are most likely to outweigh any risks when initiated within 10 years after menopause or before the age of 60. It is worth noting that cessation of therapy leads to rapid bone loss.

Cardiovascular diseases: NEUTRAL OR LOWER RISK OF CVD AND ALL-CAUSE MORTALITY

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT made little or no difference to the risk of having a coronary event (RR=1.17; 95% CI, 0.95 to 1.44), but this was based on 1 large study (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29]. Estrogen-only mHT in women who had undergone hysterectomy had a neutral effect on the risk of coronary events (RR=0.94; 95% CI, 0.78 to 1.13).

A 2024 meta-analysis of 4 studies (3 randomized controlled trials and 1 observational study) reported that there is no significant association between mHT and the incidence of heart failure in postmenopausal women (RR=1.07; 95% CI, 0.91 to 1.25)[30]. However, a meta-analysis of 2 randomized controlled trials found that mHT significantly reduced all-cause mortality in postmenopausal women with heart failure (RR=0.65; 95% CI, 0.49 to 0.87; p=0.003). Both of these studies (from 2000 and 2003) were from a time when contemporary heart failure medications were unavailable; thus it is not known if current mHT formulations have similar benefits against the backdrop of the current standard of care for heart failure patients.

In a 2020 meta-analysis of up to 26 randomized controlled trials and 47 observational studies, mHT did not significantly affect all-cause mortality (summary estimate [SE]=1.00; 95% CI, 0.96 to 1.04 in randomized controlled trials), cardiovascular mortality (SE=0.96; 95% CI, 0.83 to 1.12 in randomized controlled trials), risk of myocardial infarction (SE=1.04; 95% CI, 0.94 to 1.14 in randomized controlled trials), or risk of angina (SE=0.95; 95% CI, 0.84 to 1.08)[31]. A meta-analysis of observational studies found that mHT use was associated with a lower risk of myocardial infarction (SE=0.79; 95% CI, 0.75 to 0.84). Subgroup analyses of observational studies found a lower risk of all-cause mortality in women

using estrogen-only therapy (SE=0.85; 95% CI, 0.77 to 0.95) and in early users after menopause (SE=0.68; 95% CI, 0.51 to 0.92), but no effects were found in randomized controlled trials.

A 2024 meta-analysis of 8 randomized controlled trials including a total of 1,718 women showed that oral conjugated equine estrogens plus progestogen increased systolic blood pressure (standardized mean difference=0.60 mmHg; 95% CI, 0.19 to 1.01) [32]. However, oral or transdermal estradiol with progestogen or estradiol alone did not show any significant effects on systolic or diastolic blood pressure. Women who used oral estrogen + progestogen mHT had a higher risk of incident hypertension than never users.

Based on the 2025 recommendations from the International Menopause Society, estrogen therapy reduces coronary heart disease and all-cause mortality in women under 60 years who are recently postmenopausal and without cardiovascular disease [1]. Large clinical trials and meta-analyses have consistently shown lower mortality benefits when mHT is initiated before the age of 60 or within 10 years of menopause. Transdermal estrogen, which is associated with a lower risk of thrombosis and inflammation, may be a reasonable option for symptom relief in women with cardiovascular risk factors.

Venous thromboembolism: ORAL ESTROGEN INCREASES RISK; TRANSDERMAL ESTROGEN DOES NOT

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT increased the risk of venous thromboembolism (from 10 to 20 women in every 1000; RR=2.03, 95% CI, 1.55 to 6.64), but this was based on 1 large study (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29]. Estrogen-only mHT in women who had undergone hysterectomy also increased the risk of venous thromboembolism (RR=1.32, 95% CI, 1.00 to 1.74). These results should be interpreted carefully as they are based on one large study using oral mHT (conjugated equine estrogens with or without MPA), which may not represent the risks of the mHT currently used in clinical practice.

In a 2020 meta-analysis of up to 26 randomized controlled trials and 47 observational studies, mHT increased the risk of venous thromboembolism in randomized controlled trials (summary estimate [SE]=1.70; 95% CI, 1.33 to 2.16) and in observational studies (SE=1.32; 95% CI, 1.13 to 1.54)[31]. In a meta-analysis of randomized controlled trials, an increased risk of venous thromboembolism was observed with estrogen-progestogen mHT (SE=2.28; 95% CI, 1.64 to 3.18), in late users after menopause (SE=1.79; 95% CI, 1.39 to 2.29), and in women with underlying disease (SE=1.67; 95% CI, 1.29 to 2.17).

Based on the 2025 report from the International Menopause Society, oral estrogen therapy increases the risk of venous thromboembolism and is not recommended in women at increased risk [1]. However, transdermal estrogen therapy does not increase the risk of venous thromboembolism, even in the presence of additional risk factors (e.g., obesity, inherited thrombophilia, previous history of venous thromboembolism). For women with an intact uterus, transdermal estrogen combined with a progestogen is recommended if at high risk for venous thromboembolism. The use of a suitable progestogen is important, such as micronized progesterone, dydrogesterone, or a levonorgestrel-releasing intrauterine system.

Stroke: NEUTRAL RISK IF STARTED <10 YEARS OF MENOPAUSE OR AGE <60

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT increased the risk of stroke (from 13 to 18 women in every 1000; RR=1.39, 95% CI, 1.09 to 2.09), but this was based on 1 large study (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29]. Estrogen-only mHT in women who had undergone hysterectomy also increased the risk of stroke (RR=1.33, 95% CI, 1.06 to 1.67).

In a 2020 meta-analysis of up to 26 randomized controlled trials and 47 observational studies, mHT increased the risk of stroke in randomized controlled trials (summary estimate [SE]=1.14; 95% CI, 1.04 to 1.25) but this increase was not observed in the pooled analysis of observational studies (SE=0.98; 95% CI, 0.85 to 1.13)[31]. In subgroup analyses of randomized controlled trials, an increased risk of stroke was observed in estrogen-progestogen mHT (SE=1.14; 95% CI, 1.01 to 1.29), users with an mHT duration of ≥ 5 years (SE=1.13; 95% CI, 1.03 to 1.25), late users after menopause (SE=1.17; 95% CI, 1.01 to 1.37), and in women with an underlying disease at baseline (SE=1.14; 95% CI, 1.04 to 1.26). In subgroup analyses of the observational studies, a higher risk of stroke was seen in women taking oral mHT (SE=1.24; 95% CI, 1.11 to 1.39), whereas a lower risk of stroke was seen in women taking non-oral mHT (SE=0.86; 95% CI, 0.77 to 0.96).

Based on the 2025 recommendations from the International Menopause Society, the effects of mHT on stroke risk depends on the timing of initiation [1]. Women who initiate mHT <10 years after menopause onset or under the age of 60 are at a similar risk of stroke compared to women who do not take mHT. When initiated >10 years after menopause onset or in women over 60 years old, oral estrogen-containing mHT is associated with an increased risk of stroke, though stroke risk may vary by mHT route, dosage, and formulation. Transdermal routes and lower doses of mHT may be associated with a lower risk compared to oral or higher doses of mHT.

Breast cancer: SLIGHTLY INCREASED RISK WITH ESTROGEN-PROGESTOGEN; NEUTRAL OR LOWER RISK WITH ESTROGEN-ONLY THERAPY IN WOMEN WHO HAD A HYSTERECTOMY

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT increased the chance of developing breast cancer compared to placebo (from 19 to 24 women in every 1000; RR=1.27, 95% CI, 1.03 to 1.56), but this was based on 1 large study (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29]. Women who had undergone hysterectomy and taking estrogen-only therapy showed no difference in risk of developing breast cancer compared to placebo (RR=0.79, 95% CI, 0.61 to 1.01). These results should be interpreted carefully as they are based on one large study using oral mHT (conjugated equine estrogens with or without MPA), which may not represent the risks of the mHT currently used in clinical practice.

In a 2024 meta-analysis that examined up to 10 randomized controlled trials including a total of 14,282 postmenopausal women who had prior hysterectomy, estrogen-alone therapy showed a numerically (but not statistically) lower breast cancer incidence compared to placebo (RR=0.65; 95% CI, 0.38 to 1.11)[33]. Five clinical trials evaluated estradiol formulations, which also showed numerically lower (but statistically non-significant) breast cancer incidence (RR=0.63; 95% CI, 0.34 to 1.16).

In a 2022 meta-analysis of 4 randomized controlled trials in a total of 4,050 breast cancer survivors, mHT significantly increased the risk of breast cancer recurrence compared to placebo (HR=1.46; 95% CI, 1.12 to 1.19; p=0.006) [34]. mHT formulations in the 4 randomized controlled trials included conjugated equine estrogens, combined or sequential estradiol hemihydrate and norethisterone, tiboline, cyclic estradiol alone or with MPA. In a subgroup analysis, the risk of breast cancer recurrence was significantly increased in patients with hormone receptor-positive breast cancer (HR=1.8; 95% CI, 1.15 to 2.82, p=0.010), but not in those with hormone receptor-negative tumors (HR=1.19; 95% CI, 0.80 to 1.77; p=0.39).

Based on the 2025 recommendations from the International Menopause Society, breast cancer risk of mHT varies based on the mHT regimen and the woman's baseline risk, and the risk of breast cancer attributable to mHT is small and similar to, or lower than, the increased risks associated with lifestyle factors such as low physical activity, obesity, and alcohol consumption [1]. Estrogen-alone mHT is associated with a lower risk of breast cancer than the estrogen-progestogen mHT regimens. There is no difference in breast cancer risk between oral or transdermal estradiol. The increased risk of breast cancer is primarily associated with the addition of a synthetic progestogen (e.g., conjugated equine

estrogens + MPA); risk appears lower with micronized progesterone or with dydrogesterone. The data do not suggest an increase in breast cancer risk from vaginal delivery of hormones in women with no history of breast cancer. Higher breast density is associated with a higher risk of breast cancer and mHT should be used with caution.

Ovarian cancer: VERY SLIGHTLY INCREASED RISK

In a 2024 meta-analysis of up to 21 cohort studies (involving 15,313 cases and 4,564,785 participants) and 30 case-control studies (including 18,738 cases and 57,747 controls), mHT users had a higher risk of ovarian cancer based on both cohort studies (RR=1.20; 95% CI, 1.01 to 1.44) and case-control studies (RR=1.13; 95% CI, 1.04 to 1.22)[35]. Continuous estrogen-progestogen mHT was associated with a risk comparable to that of sequential estrogen-progestogen mHT. Risk for ovarian cancer increased with longer exposure time. Based on 6 cohort studies, the summary ovarian cancer risk estimates for less than 5 years of mHT use was 1.07 (95% CI, 0.96 to 1.19), 1.39 (95% CI, 1.20 to 1.62) for 5-9 years, and 1.52 (95% CI, 1.31 to 1.77) for more than 10 years. Based on 11 case-control studies, the summary ovarian cancer risk estimates were 1.04 (95% CI, 0.82 to 1.33) for less than 5 years of mHT use, 1.13 (95% CI, 0.99 to 1.29) for 5–9 years, and 1.37 (95% CI, 1.02 to 1.85) for more than 10 years. It is worth noting that when restricting the meta-analysis to recent studies (after 2006 for case-control studies and 2010 for cohort studies), the risk disappeared. These findings suggest that advancements and adjustments in mHT formulations and dosages may have possibly reduced the risk of mHT on ovarian cancer.

Based on the 2025 recommendations from the International Menopause Society, there is a very slight increase in ovarian cancer risk with estrogen-progestogen mHT [1]. In women with ovaries, there is a very slight increase in ovarian cancer risk with estrogen-only mHT taken for 5 years or longer.

In a 2023 meta-analysis of 8 mostly observational studies including a total of 4,191 ovarian cancer patients, mHT was associated with a higher overall survival (HR=0.66; 95% CI, 0.57 to 0.76; p<0.00001) compared to non-users [36]. A meta-analysis of 5 studies including a total of 613 ovarian cancer patients showed that mHT was associated with a longer progression-free survival (HR=0.73; 95% CI, 0.57 to 0.95; p=0.02). The authors noted that the meta-analyses had limitations including the low numbers of included patients for the meta-analysis.

Endometrial cancer: ESTROGEN-PROGESTOGEN THERAPY RECOMMENDED IN WOMEN WITH INTACT UTERUS TO PREVENT ENDOMETRIAL HYPERPLASIA AND CANCER

In a 2025 Cochrane meta-analysis of up to 72 trials involving a total of 40,652 postmenopausal women, unopposed estrogen-alone mHT increased the risk of endometrial hyperplasia at 1 year compared with placebo (from 5 to 22-43 events in every 1000 women; OR=5.86; 95% CI, 4.09 to 8.40)[37]. After 1 year, unopposed estrogen-alone mHT increased the risk of endometrial hyperplasia (from 6 to 40-68 events in every 1000 women; OR=8.97; 95% CI, 6.78 to 11.87). Continuous estrogen-progestogen mHT may have little or no effect on the risk of endometrial hyperplasia at 1 year. Sequential estrogen-progestogen mHT may increase the risk of endometrial hyperplasia at 1 year compared with placebo (from 2 to 6-27 events in every 1000 women; OR=5.53, 95% CI, 2.60 to 11.76) but have little to no difference in risk after 1 year. This Cochrane meta-analysis did not have enough studies with events to draw conclusions about endometrial cancer.

In women with a uterus, progestogen with a dose proportionate to the estrogen dose is recommended, based on the 2025 recommendations from the International Menopause Society [1]. Women taking mHT with cyclical progestogen for less than the recommended time per month may have an increased risk of endometrial hyperplasia and cancer, which increases with dose and duration of the mHT. When taking appropriately dosed sequential micronized progesterone, there does not appear to be an increase in endometrial cancer risk, though there is limited evidence for its use beyond 5 years.

Lung cancer: POSSIBLY NEUTRAL OR LOWER RISK BUT EVIDENCE IS INCONCLUSIVE

A 2025 Cochrane meta-analysis reported that continuous estrogen-progestogen mHT made little or no difference to the risk of having lung cancer (RR=1.06; 95% CI, 0.77 to 1.46) based on 1 randomized controlled trial (the WHIS) with 16,608 participants who initiated mHT over 10 years past menopause [29].

In a 2022 meta-analysis of 22 observational studies (13 prospective cohort studies and 9 case-control studies) including a total of 911,194 women, current mHT users had a significantly lower risk of lung cancer compared to never users [38]. Relative risk for current mHT users compared to never users in cohort studies was 0.91 (95% CI, 0.86 to 0.97), and relative risk for current mHT users in case-controlled studies was 0.75 (95% CI, 0.69 to 0.81). The main limitation of this meta-analysis is that it is composed of exclusively observational studies with no randomized controlled trials.

Pancreatic cancer: INCONCLUSIVE

In a 2023 meta-analysis of 11 cohort studies including a total of 2,712,313 women, there was no overall association between mHT users and non-users on pancreatic cancer risk (RR=0.92; 95% CI, 0.68 to 1.25)[39]. However, subgroup meta-analyses of 4 studies found that estrogen-only mHT (RR=0.77; 95% CI, 0.64 to 0.94) and estrogen-progestogen mHT (RR=0.85; 95% CI, 0.75 to 0.96) were associated with a lower risk of pancreatic cancer. There were no associations between pancreatic cancer risk and recency of mHT or mHT duration. Due to the inconsistent findings between the main analysis and the subgroup analyses, further studies are needed to investigate these associations. It is also worth highlighting that there are many confounding factors related to observational studies. One confounder is the "healthy-user" bias suggesting that women who choose to use mHT may share other healthy characteristics that positively affect pancreatic health.

Gastric cancer: ASSOCIATED WITH LOWER RISK BUT INCONCLUSIVE

In a 2022 meta-analysis of 11 observational studies with a total of 1,919,089 women, mHT use was associated with a lower risk of gastric cancer compared to those who had no mHT exposure (RR=0.72; 95% CI, 0.64 to 0.71) [40]. Subgroup analyses found that both estrogen-only mHT (RR=0.63; 95% CI, 0.51 to 0.77) and estrogen-progestogen mHT (RR=0.70; 95% CI, 0.57 to 0.87) were associated with a lower risk of gastric cancer compared to non-users. Because observational studies are not designed to determine cause versus effect, data from randomized clinical trials are needed to confirm these associations.

Colorectal cancer: INCONCLUSIVE

The WHI study reported that participants taking continuous estrogen-progestogen mHT (conjugated equine estrogens + MPA) had a lower incidence of colon cancer after a mean follow-up of 5.2 years (RR=0.63, 95% CI, 0.43 to 0.92) [3]. In the WHI follow-up study (11.6 years of total follow-up), fewer colorectal cancers were diagnosed in the continuous estrogen-progestogen mHT group compared with the placebo group (diagnoses per year=0.12% versus 0.16%; HR=0.72; 95% CI, 0.56 to 0.94; p=0.014) [41]. However, there was a numerically (but not statistically) higher number of colorectal cancer deaths with the estrogen-progestogen mHT compared to placebo (37 versus 27 deaths; HR=1.29; 95% CI, 0.78 to 2.11). In women who had a prior hysterectomy, the WHI 13.2-year follow-up study found that estrogen-alone mHT for 7.1 years did not significantly affect colorectal cancer rates compared to placebo (HR=1.13; 95% CI, 0.83 to 1.58). However, there was a numerically (but not statistically) higher colorectal cancer deaths in the estrogen-alone mHT group compared to placebo (34 versus 24; HR=1.46; 95% CI, 0.86 to 2.46)[42].

In a 2024 meta-analysis of 10 cohort studies including a total of 480,628 people, mHT use was associated with a lower risk of colorectal cancer mortality (HR=0.77; 95% CI, 0.68 to 0.87; p<0.05)[43]. There was a linear dose-response relationship, with a 3% lower risk of colorectal cancer for each additional year of mHT use (HR=0.97; 95% CI, 0.94 to 0.99; p<0.05). Pooled results of 7 cohort studies also showed a significant association between mHT use and a lower risk of all-cause mortality (HR=0.71; 95% CI, 0.54 to 0.92; p<0.05).

Based on the 2025 report from the International Menopause Society, inter-individual variability in genetic determinants of estrogen signaling may account for differential responsiveness to mHT-mediated protection, potentially influencing the observed heterogeneity in colorectal cancer outcomes [1].

Glaucoma: MAY DECREASE INTRAOCULAR PRESSURE BUT DATA ARE MIXED

Glaucoma is a leading cause of irreversible blindness and is characterized by the progressive degeneration of the optic nerve, which is often associated with elevated intraocular pressure. In a 2025 meta-analysis of 9 studies (2 randomized controlled trials and 7 observational studies) with a total of 1,024 people, mHT users had had a significantly lower intraocular pressure compared to controls (-3.84 mmHg; 95% CI, -5.41 to -2.26; p<0.01)[44]. However, there was heterogeneity across studies, likely due to variations in hormone formulations, dosages, and treatment durations. Not all studies show that mHT decreases intraocular pressure and some have shown mixed or non-significant results. For example, a 2020 meta-analysis of 9 randomized controlled trials including a total of 612 postmenopausal women reported that while mHT significantly improved ocular surface function, no significant effects were found on intraocular pressure (MD=-1.54; 95% CI, -3.39 to 0.32; p=0.10) [45].

Arthritis: ASSOCIATED WITH HIGHER RISK OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

Rheumatoid arthritis is a chronic autoimmune disorder characterized by symmetrical synovial inflammation that can culminate in progressive joint damage. Rheumatoid arthritis disproportionately affects women. In a 2026 meta-analysis of 5 observational studies, mHT use was associated with a modestly higher risk of rheumatoid arthritis compared to never-users (RR=1.15; 95% CI, 1.10 to 1.21; p<0.001) [46]. Current mHT users had a higher risk (RR=1.18; 95% CI, 1.00 to 1.37; p=0.04) compared with former mHT users (RR=1.11; 95% CI, 0.94 to 1.32; p=0.20). mHT use of 4 years or longer was associated with a higher risk of rheumatoid arthritis (RR=1.19; 95% CI, 1.07 to 1.33; p=0.002).

Osteoarthritis is a highly prevalent kind of arthritis that involves joint inflammation and architectural changes, resulting in functional damage and pain. In a 2022 meta-analysis of 13 observational studies (8 cohort, 4 cross-sectional, and 1 case-control studies) including a total of 2,573,164 people, mHT use was associated with a higher risk of knee osteoarthritis (HR=1.24; 95% CI, 1.07 to 1.45)[47]. Pooled analysis showed a statistically higher risk of knee joint replacement in mHT users (HR=1.30; 95% CI, 1.09 to 1.54). Higher risk of knee osteoarthritis was seen in current users of mHT (HR=1.40; 95% CI, 1.16 to 1.68), while the risk was not statistically higher in past users of mHT.

Safety: Risks of mHT varies by type, dose, route, timing of initiation, treatment duration, and medical history. Estrogen-progestogen mHT slightly increases breast and ovarian cancer risk. Venous thromboembolism risk varies by route and formulations.

Types of evidence:

- 23 meta-analyses or systematic reviews
- 1 systematic review and recommendations from the International Menopause Society
- FDA mHT label updates

The decision to start, continue, or stop mHT should be made carefully with a healthcare provider to balance potential benefits against harm in a tailored personalized manner, including considerations for personal medical history and risk factors [48]. Risks are lower if mHT is started within 10 years of menopause or before the age of 60.

People who have a history of blood clots (venous thromboembolism or pulmonary embolism), breast/endometrium/ovarian cancer, heart/liver/gallbladder disease, heart attack, stroke, or unexplained vaginal bleeding should not take mHT (Drugs.com). mHT should also be avoided if there is known or suspected pregnancy.

FDA label updates: In July 2025, the FDA removed the boxed warnings (cardiovascular disease, stroke, breast cancer, probable dementia) of combined estrogen-progestogen products as well as estrogen-alone and progestogen-alone products [5]. Recommendation to prescribe mHT "at the lowest effective dose for the shortest duration" has also been removed. New labels include updated guidance on initiating treatment in women younger than 60 years old or within 10 years of menopause onset to optimize benefit-to-risk balance.

Common mild adverse events: Common side effects of mHT include bloating, breast swelling or tenderness, headache, mood changes, nausea, and vaginal bleeding (WebMD.com). More serious but rare adverse events are described in the sections that follow. In a 2020 meta-analysis of 4 double-blind randomized controlled trials including a total of 277 Alzheimer's patients, 3 trials reported adverse events during the trials and the number of adverse events were similar in mHT and placebo groups [16]. All 3 studies reported vaginal bleeding in the estrogen-treated group (3%, 27.5%, and 44.0%, respectively) but not in the placebo group. Severity of vaginal bleeding was not assessed in these studies.

Breast cancer: Based on the 2025 recommendations from the International Menopause Society, breast cancer risk of mHT varies based on the mHT regimen and the woman's baseline risk, and the risk of breast cancer attributable to mHT is small and similar to, or lower than, the increased risks associated with lifestyle factors such as low physical activity, obesity, and alcohol consumption [1]. Estrogen-alone mHT is associated with a lower risk of breast cancer than the estrogen-progestogen mHT regimens. There is no difference in breast cancer risk between oral or transdermal estradiol. The increased risk of breast cancer is primarily associated with the addition of a synthetic progestogen (e.g., conjugated equine estrogens + MPA); risk appears lower with micronized progesterone or with dydrogesterone. The data do not suggest an increase in breast cancer risk from vaginal delivery of hormones in women with no history of breast cancer. Higher breast density is associated with a higher risk of breast cancer and mHT should be used with caution.

Breast cancer survivors: mHT increases the risk of breast cancer recurrence compared to placebo in breast cancer survivors, based on a meta-analysis of randomized controlled trials [34]. mHT formulations in the 4 randomized controlled trials included conjugated equine estrogens, combined or sequential estradiol hemihydrate and norethisterone, tiboline, cyclic estradiol alone or with MPA. The risk of breast cancer recurrence was significantly increased in patients with hormone receptor-positive breast cancer, but not in those with hormone receptor-negative tumors.

Ovarian cancer: Based on the 2025 recommendations from the International Menopause Society, there is a very slight increase in ovarian cancer risk with estrogen-progestogen mHT [1]. In women with ovaries, there is a very slight increase in ovarian cancer risk with estrogen-only mHT taken for 5 years or longer.

Venous thromboembolism: The risk of venous thromboembolism varies based on route and formulations. Based on the 2025 recommendations from the International Menopause Society, oral estrogen therapy increases the risk of venous thromboembolism and is not recommended in women at increased risk [1]. However, transdermal estrogen therapy does not increase the risk of venous thromboembolism, even in the presence of additional risk factors (e.g., obesity, inherited thrombophilia, previous history of venous thromboembolism). For women with an intact uterus, transdermal estrogen is recommended if at high risk for venous thromboembolism, combined with a progestogen. The use of a suitable progestogen is important, such as micronized progesterone, dydrogesterone, or a levonorgestrel-releasing intrauterine system.

SAFETY BY TYPES OF MHT:

Estrogen-progestogen versus estrogen-alone therapy: In women with an intact uterus experiencing menopausal symptoms, estrogen should always be given with a progestogen due to estrogen's stimulatory effects on the endometrium. Estrogen-alone mHT is typically prescribed in women with a prior hysterectomy. In women with an intact uterus, unopposed estrogen promotes the growth of the endometrium which can lead to endometrial hyperplasia and possibly cancer over the long-term [1; 37].

Conjugated equine estrogens-progestogen versus estradiol-progestogen therapy: Conjugated equine estrogens are created from the urine of pregnant mares and contain estrogen sulfate and at least 10 other hormones, some of which are not naturally found in humans. In contrast, estradiol is the dominant endogenous estrogen before menopause in women. Oral conjugated equine estrogens + MPA (Prempro) was tested in the large WHIS study that found increased risks of dementia, breast cancer, heart disease, stroke, and venous thromboembolism in older women who initiated mHT over 10 years past menopause [3; 4]. In contrast, the KEEPS randomized placebo-controlled clinical trial that enrolled women within 3 years of menopause found that oral conjugated equine estrogens (Premarin, 0.45 mg/day), transdermal bioidentical estrogen (17β-estradiol; Climara, 50 µg/day), or placebo, combined with progesterone (Prometrium) for 4 years did not benefit or harm cognitive functions compared to placebo; there was no significant difference in cognitive functions between conjugated equine estrogens + progesterone versus transdermal estradiol + progesterone [7]. A 2024 meta-analysis of 8 randomized controlled trials including a total of 1,718 women showed that oral conjugated equine estrogens plus progestogen increased systolic blood pressure (standardized mean difference=0.60 mmHg; 95% CI, 0.19 to 1.01) [32]. However, estradiol (oral or transdermal) with progestogen or estradiol alone did not significantly affect systolic or diastolic blood pressure.

MPA versus progesterone: Medroxyprogesterone acetate (MPA) is a synthetic progestogen and was used in combination with conjugated equine estrogens in the WHIS study that found increased risks of dementia, breast cancer, heart disease, stroke, and venous thromboembolism in older women who initiated mHT over 10 years past menopause [3; 4]. In contrast, progesterone is the natural progestogen produced in the human body. The increased risk of breast cancer with mHT is primarily associated with the addition of a synthetic progestogen (e.g., conjugated equine estrogens + MPA); risk appears lower with micronized progesterone or with dydrogesterone [1]. In hippocampal cell cultures, MPA can antagonize the neuroprotective effects of estradiol, in contrast to endogenous progesterone [49].

Oral vs transdermal estrogen: Oral versus transdermal estrogen can have different effects. Oral estrogen has low systemic bioavailability due to gut and liver (first-pass) metabolism, with estradiol converted to estrone by the liver [50]. Transdermal estrogen bypasses this first-pass effect, resulting in higher concentrations of estradiol. The risk of venous thromboembolism is different between oral versus transdermal estrogen therapy. Based on the 2025 recommendations from the International Menopause Society, oral estrogen therapy increases the risk of venous thromboembolism and is not recommended in women at increased risk [1]. However, transdermal estrogen therapy does not increase the risk of venous thromboembolism, even in the presence of additional risk factors (e.g., obesity, inherited thrombophilia, previous history of venous thromboembolism). There is no difference in breast cancer risk between oral or transdermal estradiol [1].

In a 2026 meta-analysis of 8 randomized controlled trials including a total of 885 women, oral estrogen therapy resulted in a higher mean change in HDL-cholesterol levels (MD=3.48 mg/dL; 95% CI, 1.54 to 5.43; $p<0.01$) compared to transdermal estrogen therapy [51]. Oral estrogen therapy also resulted in a significant increase in mean triglyceride levels (MD=19.82; 95% CI, 6.85 to 32.78; $p<0.01$) compared to transdermal estrogen therapy. There were no significant differences between oral estrogen therapy and transdermal estrogen therapy on mean changes in systolic or diastolic blood pressure, heart rate, total cholesterol, or LDL-cholesterol levels.

Compounded bioidentical hormone therapy: Based on the 2025 recommendations from the International Menopause Society, compounded bioidentical hormone therapy is not recommended due to safety and efficacy concerns, including a lack of quality control and rigorous regulatory oversight, and absence of scientific evidence of safety, purity, and efficacy [1]. Compounded bioidentical hormone therapies are not standardized and do not undergo the strict regulatory processes as approved mHTs.

SAFETY OF SPECIFIC ESTROGEN-PROGESTOGEN FORMULATIONS:

Bijuva (estradiol + progesterone capsule): Bijuva is an estradiol/progesterone capsule approved for the treatment of moderate to severe hot flushes in women with a uterus. Bijuva has an updated prescribing information (February 2026) after the FDA removed the black box warnings of some mHT formulations. Bijuva is contraindicated in undiagnosed abnormal genital bleeding, breast cancer or history of breast cancer, estrogen-dependent neoplasia, active deep vein thrombosis or pulmonary embolism, active or history of arterial thromboembolic disease, hepatic impairment, or known thrombophilic disorders (protein C, protein S or antithrombin deficiency)(Bijuva prescribing information). The most common adverse reactions with Bijuva are breast tenderness, headache, nausea, vaginal bleeding, vaginal discharge, and pelvic pain. Warnings and precautions include cardiovascular disorders (pulmonary embolisms, deep vein thrombosis, stroke, myocardial infarction), malignant neoplasms (breast cancer), gallbladder disease, hypercalcemia, vision loss, hypertriglyceridemia, and cholestatic jaundice. Bijuva has 41 major, 375 moderate, and 23 minor drug interactions based on Drugs.com. Inducers of CYP3A4 such as St. John's wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens and progestogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of the estrogen or the progestogen or both and may result in adverse reactions.

Climara Pro (estradiol + levonorgestrel patch): Climara Pro is an estradiol/levonorgestrel skin patch approved for the treatment of menopausal symptoms such as hot flashes and to prevent osteoporosis in menopausal women (Drugs.com). Climara Pro should not be used in women who have had a hysterectomy, or have liver disease, a bleeding disorder, unusual vaginal bleeding, a history of breast or uterine cancer, or in women who have ever had a heart attack, stroke, blood clot, or plan to have major surgery. Common side effects of Climara Pro include nausea, vomiting, bloating, stomach cramps, headache, breast pain, hair loss, and vaginal itching, discharge, or breakthrough bleeding. More serious but less common adverse events may include heart attack symptoms, signs of a stroke (numbness/weakness), signs of a blood clot in the lung or leg, vomiting, jaundice, unusual vaginal bleeding, a lump in the breast, and high levels of calcium in the blood. Climara Pro has 77 major, 372 moderate, and 29 minor drug interactions based on Drugs.com. These drug interactions include those with St. John's wort, antibiotics, antifungal medications, heart or blood pressure medicine, antiviral medications to treat hepatitis or HIV/AIDS, seizure medications, and tuberculosis medications.

Activella (estradiol + norethindrone acetate tablet): Activella (other brand names of this formulation include Lopreeza and Mimvey) is an estradiol/norethindrone oral tablet approved for the treatment of

moderate to severe symptoms of menopause and is also used to prevent osteoporosis after menopause (Drugs.com). Activella should not be taken by people with undiagnosed abnormal genital bleeding, known/suspected/history of breast cancer, estrogen-dependent cancers, active/history of deep vein thrombosis or pulmonary embolism, active arterial thromboembolic disease (stroke, myocardial infarction), liver impairment/disease, or known thrombophilic disorders (known protein C, protein S, or antithrombin deficiency)(Activella prescribing information from 2020). Most common adverse reactions are back pain, headache, pain in the extremity, nausea, diarrhea, gastroenteritis, insomnia, emotional lability, upper respiratory tract infection, weight increase, breast pain, postmenopausal bleeding, uterine fibroid, vaginal hemorrhage, ovarian cyst, endometrial thickening, viral infection, moniliasis genital, and accidental injury. Warnings of serious but rare adverse events include deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, and invasive breast cancer. Drug interactions include inducers and/or inhibitors of CYP3A4, which may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and result in side effects.

Angeliq (estradiol + drospirenone tablet): Angeliq is an estradiol/drospirenone oral tablet approved for the treatment of menopausal symptoms such as hot flushes, vaginal dryness, burning, and irritation (Drugs.com). Angeliq should not be used in women who have had a hysterectomy, breast cancer, estrogen-dependent cancer, heart attack, stroke, deep vein thrombosis, pulmonary embolism, or have coronary artery disease, a bleeding disorder, undiagnosed vaginal bleeding, kidney disease, liver disease, an adrenal gland disorder, or thrombophilic disorders (protein C, protein S, or antithrombin deficiency)(Angeliq prescribing information from 2023). Angeliq should not be used if pregnant. Cigarette smoking should be avoided as it can greatly increase the risk of blood clots, stroke, or heart attack while taking Angeliq. Common side effects of Angeliq include gastrointestinal and abdominal pain, genital tract bleeding, breast pain and discomfort, and headache. Angeliq can increase the risk of blood clots, stroke, heart attack, gallbladder disease, and cancer of the breast, uterus, or ovaries. Angeliq contains the progestogen drospirenone, which has anti-aldosterone activity, including the potential of hyperkalemia in high-risk patients. There are 571 drugs known to interact with Angeliq, with 95 major, 452 moderate, and 24 minor interactions (Drugs.com). There is a potential for an increase in serum potassium in women taking drospirenone with other drugs that may affect electrolytes, such as ACE inhibitors, angiotensin receptor blockers, or NSAIDs, which is more pronounced in diabetic women (Angeliq prescribing information from 2023). Inducers of CYP3A4 such as St. John's wort, phenobarbital,

carbamazepine, and rifampin may reduce plasma concentrations of estrogens and progestins, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g.,, clarithromycin, erythromycin), diltiazem, and grapefruit juice increased the plasma concentrations of the estrogen or the progestin or both.

CombiPatch (estradiol + norethindrone acetate patch): CombiPatch is an estradiol/norethindrone acetate transdermal patch used to treat moderate to severe hot flushes and other symptoms of menopause. Warnings of CombiPatch include cardiovascular disorders (increased risk of pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction), breast cancer, endometrial cancer, ovarian cancer, and probable dementia in women over 65 (CombiPatch prescribing information from 2024). CombiPatch should not be used during pregnancy or in women who have had a hysterectomy. CombiPatch should not be used in women who have unusual vaginal bleeding, have had breast or uterine cancer, had a stroke or heart attack, currently have or have had blood clots, liver problems, or a bleeding disorder. Common side effects include headache, breast pain, irregular vaginal bleeding or spotting, stomach or abdominal cramps, bloating, nausea, vomiting, hair loss, fluid retention, vaginal yeast infection, and redness or irritation at patch placement site. Serious but less common side effects include a heart attack, stroke, blood clots, dementia, breast cancer, endometrial cancer, ovarian cancer, high blood pressure, high blood sugar, gallbladder disease, liver problems, changes in thyroid hormone levels, enlargement of benign tumors of the uterus (fibroids), and depression. Drug interaction studies have not been conducted with CombiPatch. Because estrogens are metabolized partially by CYT3A4, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort preparations, anticonvulsants (e.g., phenobarbital, phenytoin and carbamazepine), phenylbutazone, and anti-infectives (e.g., rifampin, rifabutin, nevirapine and efavirenz) may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Prempro (conjugated equine estrogens + MPA tablet): Prempro is a tablet containing conjugated equine estrogens and MPA; it is approved for the treatment of menopausal symptoms such as hot flushes and vaginal changes and to prevent osteoporosis in menopausal women. Warnings of Prempro include cardiovascular disorders (increased risks of stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction), breast cancer, endometrial cancer, and probable dementia in women over 65

(Prempro prescribing information from 2025). Prempro should not be used in people with undiagnosed abnormal genital bleeding, breast cancer, estrogen-dependent cancer, deep vein thrombosis, pulmonary embolism, arterial thromboembolic disease (stroke and myocardial infarction), liver disease, or thrombophilic disorders (protein C, protein S, or antithrombin deficiency). The most common adverse reactions are abdominal pain, asthenia, back pain, headache, flatulence, nausea, depression, pruritis, breast pain, dysmenorrhea, and leukorrhea. Estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in side effects. Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

Sources and dosing:

For women with prior hysterectomy who have moderate to severe symptoms of menopause, doctors may prescribe a low dose estrogen, which comes in different forms including pills, patches, vaginal rings, gels, or sprays (WebMD.com; [1]). For people with an intact uterus, a combination hormone therapy including estrogen and progesterone is prescribed to prevent endometrial hyperplasia.

The terms "estrogens" and "progestogens" encompasses a broad range of natural and synthetic molecules that affect the estrogen and progesterone receptors. Different types of hormone therapy can have different effects. Estrogens naturally found in the human body include 17β-estradiol, estrone, estriol, and 17α-estradiol. 17β-estradiol is the dominant natural estrogen before menopause.

Below is a list of common menopausal hormone therapies that are approved in the US as of February 2026. Products in gray text include conjugated equine estrogens as their primary active ingredients, with or without a progestogen or an estrogen receptor modulator. Conjugated equine estrogens are created from the urine of pregnant mares and contain estrogen sulfate and at least 10 other hormones, some of which are not naturally found in humans. Those in purple text are combinations of estradiol (predominant estrogen before menopause in women) and a form of natural or synthetic progestogen. Those in blue text are topical products that contain estradiol alone.

Product (US)	Active ingredient(s)	Dose(s)	Manufacturer	Route
Premarin	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25 mg tablets	Wyeth (Pfizer)	Oral
Premarin Vaginal Cream	Conjugated estrogens	0.625 mg/g cream	Wyeth (Pfizer)	Vaginal
Prempro	Conjugated estrogens + medroxyprogesterone acetate	Tablets: 0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5 mg	Wyeth (Pfizer)	Oral
Premphase	Conjugated estrogens + medroxyprogesterone acetate	Sequential pack: 0.625 mg CE (days 1–14) then 0.625/5 mg CE/MPA (days 15–28)	Wyeth (Pfizer)	Oral (sequential)
Duavee	Conjugated estrogens + bazedoxifene	0.45/20 mg tablet	Wyeth (Pfizer)	Oral
Activella	Estradiol + norethindrone acetate	1/0.5 mg and 0.5/0.1 mg tablets	Amneal	Oral
Angeliq	Estradiol + drospirenone	0.25 mg estradiol / 0.5 mg drospirenone; 0.5 mg estradiol / 1 mg drospirenone tablet	Bayer	Oral
Bijuva	Estradiol + progesterone	Capsules: 0.5/100 mg and 1/100 mg	Mayne Pharma	Oral
Climara Pro	Estradiol + levonorgestrel	Patch delivers 0.045 mg/day E2 + 0.015 mg/day LNG (contains 4.4 mg E2 + 1.39 mg LNG)	Bayer	Transdermal patch

CombiPatch	Estradiol + norethindrone acetate	Patch delivers 0.05/0.14 mg/day or 0.05/0.25 mg/day	Noven	Transdermal patch
Minivelle	Estradiol	Patch delivers 0.025, 0.0375, 0.05, 0.075, 0.1 mg/day	Noven	Transdermal patch
Menostar	Estradiol	Patch delivers 14 mcg/day (0.014 mg/day)	Bayer	Transdermal patch
Divigel	Estradiol	Single-dose packets: 0.25, 0.5, 0.75, 1.0, 1.25 mg estradiol	Vertical	Topical gel (transdermal)
Estrace	Estradiol	0.5 mg, 1 mg, or 2 mg tablets	AbbVie	Oral
EstroGel	Estradiol	Metered pump: 0.75 mg estradiol per pump (1.25 g of 0.06% gel)	Ascend	Topical gel (transdermal)
Evamist	Estradiol	Metered spray: 1.53 mg estradiol per spray (90 µL)	Padagis	Topical spray (transdermal)
Estrasorb	Estradiol (as estradiol hemihydrate)	2.5 mg estradiol per g; pouch = 1.74 g emulsion (label dosing is two pouches daily)	Exeltis	Topical emulsion (transdermal)
Femring	Estradiol acetate	Vaginal ring: 0.05 mg/day or 0.10 mg/day	Millicent US	Vaginal ring
Imvexxy	Estradiol	Vaginal insert: 4 µg or 10 µg	Mayne Pharma	Vaginal insert

Research underway:

There are numerous studies testing mHTs in clinical trials, based on ClinicalTrials.gov, though many of these studies use the mHT as the standard-of-care control intervention while testing other interventions. There is currently one large ongoing clinical trial in 600 postmenopausal women that is testing the effects of various formulations of mHTs (oral, transdermal, SERMS, aromatase inhibitors, etc.) on blood levels of Aβ42 (NCT04312399). This study is scheduled to be completed in December 2028.

While outside the scope of this report, a new class of neurokinin-targeted therapies (non-hormonal treatments) are under development and neurokinin receptor antagonists reduce the frequency and severity of vasomotor symptoms in postmenopausal women by modulating kisspeptin, neurokinin B, and dynorphin neurons in the hypothalamus. For example, elinzanetant, a dual NK1 and NK3 receptor antagonist, has shown significant efficacy in reducing both the frequency and severity of vasomotor symptoms [52].

A topic discussed in a separate report is phytoestrogen-based therapies (see Soy Isoflavones report). Soy isoflavones include genistein, genistin (glycoside, or sugar-bound form of genistein), dihydrogenistein (metabolite of genistein), daidzein, daidzin (glycoside of daidzein), equol (metabolite of daidzein), glycitein, glycitin (glycoside of glycitein), and dihydroglycitein (metabolite of glycitein). Soy isoflavones are one of the main classes of phytoestrogens, and they are able to interact with estrogen receptors, thus drawing attention for women's health, particularly for prevention of menopausal symptoms (e.g., hot flashes, cognitive symptoms), breast pain, breast cancer, and premenstrual syndrome (PMS)(WebMD.com).

Search terms:

Pubmed, Google: menopausal hormone therapy, hormone replacement therapy

Websites visited for: menopausal hormone therapy, hormone replacement therapy

- ClinicalTrials.gov
- Examine.com
- Drugs.com (Activella; Angeliq; Bijuva; Climara Pro; Combipatch; Estrace)
- WebMD.com
- PubChem (estradiol; progesterone)

- DrugBank.ca (estradiol; progesterone)
- Labdoor.com (0)
- ConsumerLab.com (0)

References:

1. Panay N, Fenton A, Hamoda H *et al.* (2025) International Menopause Society (IMS) recommendations and key messages on women's midlife health and menopause. *Climacteric : the journal of the International Menopause Society* 28, 634-656.http://www.ncbi.nlm.nih.gov/pubmed/41433054

2. Greendale GA, Huang MH, Wight RG *et al.* (2009) Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology* 72, 1850-1857.http://www.ncbi.nlm.nih.gov/pubmed/19470968

3. Rossouw JE, Anderson GL, Prentice RL *et al.* (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288, 321-333.http://www.ncbi.nlm.nih.gov/pubmed/12117397

4. Shumaker SA, Legault C, Rapp SR *et al.* (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 289, 2651-2662.http://www.ncbi.nlm.nih.gov/pubmed/12771112

5. Makary MA, Nguyen CP, Hoeg TB *et al.* (2026) Updated Labeling for Menopausal Hormone Therapy. *JAMA* 335, 117-118.http://www.ncbi.nlm.nih.gov/pubmed/41212720

6. Gleason CE, Dowling NM, Kara F *et al.* (2024) Long-term cognitive effects of menopausal hormone therapy: Findings from the KEEPS Continuation Study. *PLoS Med* 21, e1004435.http://www.ncbi.nlm.nih.gov/pubmed/39570992

7. Gleason CE, Dowling NM, Wharton W *et al.* (2015) Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. *PLoS Med* 12, e1001833; discussion e1001833.http://www.ncbi.nlm.nih.gov/pubmed/26035291

8. Henderson VW, John JA, Hodis HN *et al.* (2016) Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology* (Epub ahead of print)

9. Andy C, Nerattini M, Jett S *et al.* (2024) Systematic review and meta-analysis of the effects of menopause hormone therapy on cognition. *Frontiers in endocrinology* 15, 1350318.http://www.ncbi.nlm.nih.gov/pubmed/38501109

10. Resnick SM, Espeland MA, Jaramillo SA *et al.* (2009) Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology* 72, 135-142.http://www.ncbi.nlm.nih.gov/pubmed/19139364

11. Espeland MA, Shumaker SA, Leng I *et al.* (2013) Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA internal medicine* 173, 1429-1436.http://www.ncbi.nlm.nih.gov/pubmed/23797469

12. Kantarci K, Kara F, Tosakulwong N *et al.* (2026) Long-term amyloid PET and MRI outcomes in a menopausal hormone therapy trial. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 22, e71067.http://www.ncbi.nlm.nih.gov/pubmed/41618732

13. Nerattini M, Jett S, Andy C *et al.* (2023) Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia. *Frontiers in aging neuroscience* 15, 1260427.http://www.ncbi.nlm.nih.gov/pubmed/37937120

14. Melville M, He L, Desai R *et al.* (2025) Menopause hormone therapy and risk of mild cognitive impairment or dementia: a systematic review and meta-analysis. *The lancet Healthy longevity* 6, 100803.http://www.ncbi.nlm.nih.gov/pubmed/41448220

15. Wu M, Li M, Yuan J *et al.* (2020) Postmenopausal hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease: A systematic review and time-response meta-analysis. *Pharmacological research* 155, 104693.http://www.ncbi.nlm.nih.gov/pubmed/32057896

16. Zhou C, Wu Q, Wang Z *et al.* (2020) The Effect of Hormone Replacement Therapy on Cognitive Function in Female Patients With Alzheimer's Disease: A Meta-Analysis. *American journal of Alzheimer's disease and other dementias* 35, 1533317520938585.http://www.ncbi.nlm.nih.gov/pubmed/32677442

17. Hogervorst E, Yaffe K, Richards M *et al.* (2009) Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev*, CD003799.http://www.ncbi.nlm.nih.gov/pubmed/19160224

18. Thurston RC, Maki P, Chang Y *et al.* (2024) Menopausal vasomotor symptoms and plasma Alzheimer disease biomarkers. *American journal of obstetrics and gynecology* 230, 342 e341-342 e348.http://www.ncbi.nlm.nih.gov/pubmed/37939982

19. Coughlan GT, Rubinstein Z, Klinger H *et al.* (2025) Associations between hormone therapy use and tau accumulation in brain regions vulnerable to Alzheimer's disease. *Science advances* 11, eadt1288.http://www.ncbi.nlm.nih.gov/pubmed/40043125

20. Wisch JK, Meeker KL, Gordon BA *et al.* (2021) Sex-related Differences in Tau Positron Emission Tomography (PET) and the Effects of Hormone Therapy (HT). *Alzheimer disease and associated disorders* 35, 164-168.http://www.ncbi.nlm.nih.gov/pubmed/32520734

21. Wang YT, Therriault J, Tissot C *et al.* (2024) Hormone therapy is associated with lower Alzheimer's disease tau biomarkers in post-menopausal females -evidence from two independent cohorts. *Alzheimer's research & therapy* 16, 162.http://www.ncbi.nlm.nih.gov/pubmed/39034389

22. Hara Y, Waters EM, McEwen BS *et al.* (2015) Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiological reviews* 95, 785-807.http://www.ncbi.nlm.nih.gov/pubmed/26109339

23. Yao J, Brinton RD (2012) Estrogen regulation of mitochondrial bioenergetics: implications for prevention of Alzheimer's disease. *Advances in pharmacology* 64, 327-371.http://www.ncbi.nlm.nih.gov/pubmed/22840752

24. Strom JO, Ingberg E (2014) Impact of methodology on estrogens' effects on cerebral ischemia in rats: an updated meta-analysis. *BMC neuroscience* 15, 22.http://www.ncbi.nlm.nih.gov/pubmed/24495535

25. Singh M, Su C (2013) Progesterone and neuroprotection. *Hormones and behavior* 63, 284-290.http://www.ncbi.nlm.nih.gov/pubmed/22732134

26. Jauregi-Zinkunegi A, Gleason CE, Bendlin B *et al.* (2025) Menopausal hormone therapy is associated with worse levels of Alzheimer's disease biomarkers in APOE epsilon4-carrying women: An observational study. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 21, e14456.http://www.ncbi.nlm.nih.gov/pubmed/39783876

27. Saleh RNM, Hornberger M, Ritchie CW *et al.* (2023) Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort. *Alzheimer's research & therapy* 15, 10.http://www.ncbi.nlm.nih.gov/pubmed/36624497

28. Tang Y, Ma R, Zhang L *et al.* (2025) Effectiveness and safety of hormone replacement therapy in the treatment of menopausal syndrome: a meta-analysis. *American journal of translational research* 17, 1-15.http://www.ncbi.nlm.nih.gov/pubmed/39959227

29. Bofill Rodriguez M, Yong LN, Mirkov S *et al.* (2025) Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 11, CD004143.http://www.ncbi.nlm.nih.gov/pubmed/41307293

30. Arayici ME, Kilic ME, Yilmaz MB (2024) The Impact of Hormone Replacement Therapy on the Risk of Heart Failure in Postmenopausal Women: A Meta-Analysis of Clinical and Observational Studies. *Pharmacoepidemiology and drug safety* 33, e70029.http://www.ncbi.nlm.nih.gov/pubmed/39375997

31. Kim JE, Chang JH, Jeong MJ *et al.* (2020) A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. *Scientific reports* 10, 20631.http://www.ncbi.nlm.nih.gov/pubmed/33244065

32. Ferreira Campos L, de Andrade Costa G, Domingues Feitosa M *et al.* (2024) Effect of hormone therapy on blood pressure and hypertension in postmenopausal women: a systematic review and meta-analysis. *Menopause* 31, 556-562.http://www.ncbi.nlm.nih.gov/pubmed/38688468

33. Chlebowski RT, Aragaki AK, Pan K *et al.* (2024) Randomized trials of estrogen-alone and breast cancer incidence: a meta-analysis. *Breast cancer research and treatment* 206, 177-184.http://www.ncbi.nlm.nih.gov/pubmed/38653905

34. Poggio F, Del Mastro L, Bruzzone M *et al.* (2022) Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast cancer research and treatment* 191, 269-275.http://www.ncbi.nlm.nih.gov/pubmed/34731351

35. Xiang H, Wang L, Sun L *et al.* (2024) The risk of ovarian cancer in hormone replacement therapy users: a systematic review and meta-analysis. *Frontiers in endocrinology* 15, 1414968.http://www.ncbi.nlm.nih.gov/pubmed/39086900

36. Achimas-Cadariu PA, Paun DL, Pasca A (2023) Impact of Hormone Replacement Therapy on the Overall Survival and Progression Free Survival of Ovarian Cancer Patients: A Systematic Review and Meta-Analysis. *Cancers* 15.http://www.ncbi.nlm.nih.gov/pubmed/36672307

37. Kim D, Jordan V, Casciola F *et al.* (2025) Hormone therapy in postmenopausal women and risk of endometrial hyperplasia or endometrial cancer. *Cochrane Database Syst Rev* 10, CD000402.http://www.ncbi.nlm.nih.gov/pubmed/41128095

38. Wen H, Lin X, Sun D (2022) The association between different hormone replacement therapy use and the incidence of lung cancer: a systematic review and meta-analysis. *Journal of thoracic disease* 14, 381-395.http://www.ncbi.nlm.nih.gov/pubmed/35280481

39. Jang YC, Leung CY, Huang HL (2023) Association of Menopausal Hormone Therapy with Risk of Pancreatic Cancer: A Systematic Review and Meta-analysis of Cohort Studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 32, 114-122.http://www.ncbi.nlm.nih.gov/pubmed/36306390

40. Jang YC, Leung CY, Huang HL (2022) Association of hormone replacement therapy with risk of gastric cancer: a systematic review and meta-analysis. *Scientific reports* 12, 12997.http://www.ncbi.nlm.nih.gov/pubmed/35906381

41. Simon MS, Chlebowski RT, Wactawski-Wende J *et al.* (2012) Estrogen plus progestin and colorectal cancer incidence and mortality. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 30, 3983-3990.http://www.ncbi.nlm.nih.gov/pubmed/23008295

42. Lavasani S, Chlebowski RT, Prentice RL *et al.* (2015) Estrogen and colorectal cancer incidence and mortality. *Cancer* 121, 3261-3271.http://www.ncbi.nlm.nih.gov/pubmed/26036212

43. Liu K, He Y, Li Q *et al.* (2024) Impact of hormone replacement therapy on all-cause and cancer-specific mortality in colorectal cancer: A systematic review and dose–response meta-analysis of observational studies. *Journal of evidence-based medicine* 17, 377-389.http://www.ncbi.nlm.nih.gov/pubmed/38943605

44. Safarpour Lima B, Sayanjali S, Shoham-Hazon N (2025) Effect of estrogen and progesterone therapy on intraocular pressure: a systematic review and meta-analysis study. *European journal of translational myology* 35.http://www.ncbi.nlm.nih.gov/pubmed/40341753

45. Hao Y, Xiaodan J, Jiarui Y *et al.* (2020) The effect of hormone therapy on the ocular surface and intraocular pressure for postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. *Menopause* 27, 929-940.http://www.ncbi.nlm.nih.gov/pubmed/32520901

46. Guimaraes C, Balbinot E, Marcal F *et al.* (2026) Hormone therapy in menopause increases rheumatoid arthritis risk: A systematic review and meta-analysis. *Seminars in arthritis and rheumatism* 77, 152935.http://www.ncbi.nlm.nih.gov/pubmed/41619569

47. Hou WY, Zhu CY, Gu YF *et al.* (2022) Association of hormone replacement therapy and the risk of knee osteoarthritis: A meta-analysis. *Medicine* 101, e32466.http://www.ncbi.nlm.nih.gov/pubmed/36595852

48. The Hormone Therapy Position Statement of The North American Menopause Society" Advisory P (2022) The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 29, 767-794.http://www.ncbi.nlm.nih.gov/pubmed/35797481

49. Nilsen J, Brinton RD (2003) Divergent impact of progesterone and medroxyprogesterone acetate (Provera) on nuclear mitogen-activated protein kinase signaling. *Proc Natl Acad Sci U S A* 100, 10506-10511.https://www.ncbi.nlm.nih.gov/pubmed/12925744

50. O'Connell MB (1995) Pharmacokinetic and pharmacologic variation between different estrogen products. *Journal of clinical pharmacology* 35, 18S-24S.http://www.ncbi.nlm.nih.gov/pubmed/8530713

51. Doma M, Loayza Pintado JJ, Atwal A *et al.* (2026) Efficacy of oral versus transdermal estrogen therapy on cardiovascular and lipid parameters among postmenopausal women: a systematic review and meta-analysis of randomized clinical trials. *Menopause* 33, 242-250.http://www.ncbi.nlm.nih.gov/pubmed/41186572

52. Afifi E, Abdelaziz Ismail R, Ashraf Aldbash A *et al.* (2026) Elinzanetant: Efficacy and safety in the management of vasomotor symptoms in postmenopausal women, a systematic review and meta-analysis with grading of recommendations assessment, development, and evaluation assessment. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*.http://www.ncbi.nlm.nih.gov/pubmed/41732998